Anterior Cutaneous Nerve Entrapment Syndrome (ACNES)

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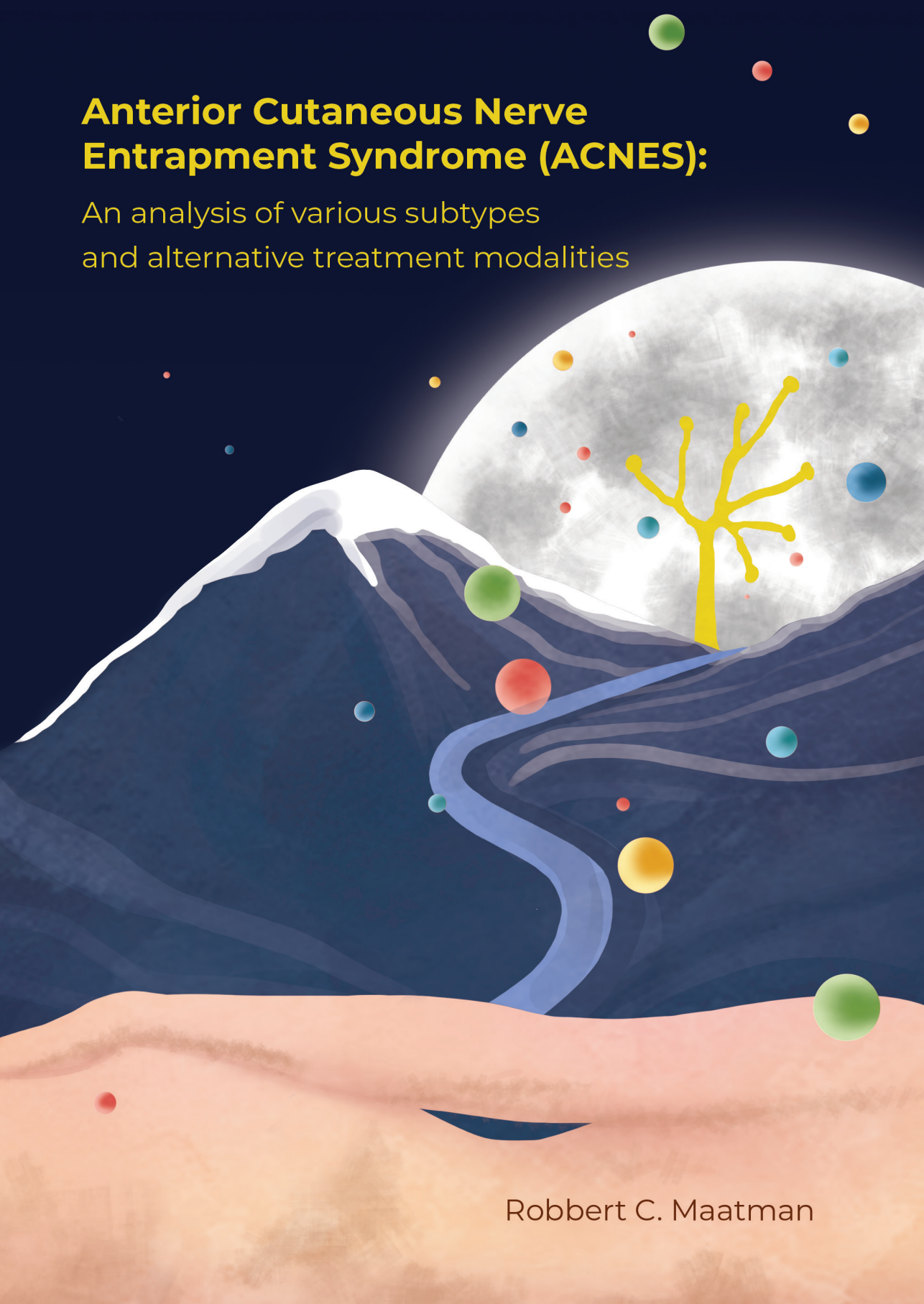
An analysis of various subtypes and alternative treatment modalities



Robbert C. Maatman

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Dr. J.P.J. Burgmans, Diakonessenhuis Zeist

Voor mijn ouders

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CHAPTER 1

Introduction and outline

INTRODUCTION TO THE ACNES SYNDROME

Chronic abdominal pain (CAP) of uncertain etiology is a common clinical entity and a diagnostic challenge for a variety of physicians including general practitioners, surgeons, pediatricians, gastro-enterologists and pain specialists. These patients may undergo multiple imaging modalities, sometimes even diagnostic laparoscopic or open surgeries, to identify the underlying cause of the abdominal pain. However, even these highly invasive methods may not always lead to a diagnostic success[1,2].

CAP may be due to an abdominal *wall* related origin. Several studies have demonstrated that up to 30% of patients with CAP of an unknown source in fact suffer from an abnormality in the abdominal wall[3-5]. A classic example of a chronic abdominal wall pain (CAWP) is the anterior cutaneous nerve entrapment syndrome (ACNES). In ACNES, terminal branches of thoracic intercostal nerves are thought to be "entrapped" by a hitherto unidentified event, leading to severe neuropathic pain in anterior portions of the trunk[6]. Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as 'pain caused by a (demonstrable) lesion or disease of the somatosensory nervous system'[7]. Since thoracic intercostal nerves are possibly entrapped in ACNES, the related pain can be classified as a neuropathic type pain. The differentiation between neuropathic and nociceptive pain is challenging. However, neuropathic signs and symptoms may be suspected during history taking and by using specific questionnaires such as DN-4, or during simple tests during physical examination[8-10].

Nowadays, most physicians consider themselves experts in 'visceral thinking'. Therefore a suspicion on an abdominal wall origin of the debilitating pain is rarely raised. In previous eras well before the widespread introduction of imaging techniques, these thoughts were different. As early as the year of 1792, 'peritonitis muscularis' was brought to the attention by Frank[11]. In fact, he was describing a painful condition originating in the abdominal wall that was easily mistaken as 'visceral pain'. Cyriax described in 1919 a "neuralgia of the intercostal nerves'' that mimicked visceral disease[12]. Later on, the surgeon Carnett reported that the abdominal wall itself could very well lead to abdominal pain (Figure 1.1)[13]. He introduced a simple two-stage test potentially discriminating between visceral pain and abdominal wall pain. First, the point or area of maximal pain is identified by deep palpation using a fingertip. Subsequently, pressure on the painful point is released and the patient is asked to lift his or her head for tensing of the abdominal muscles. Deep palpation at the point of maximal pain is then repeated. If both stages lead to a predictable and recognizable pain, its origin is probably located in the abdominal wall rather than in the visceral cavity[1,13]. Conversely, only pain during the first stage of Carnett's test may be related to a diseased viscus. The clinical validity of this Carnett test demonstrating an abdominal wall source of CAP has repeatedly been confirmed[1,3,4].

Figure 1.1:
John Berton Carnett (1890-1988).

Anatomy of thoracic spinal nerves

The abdominal wall is sensorily innervated by a network of nerve branches arising from the thoracic spinal nerves (T7-T12)[14]. These thoracic spinal nerves exit the vertebral canal and subsequently divide into a dorsal ramus which in turn splits into a medial and lateral branch, and an anterior ramus that further continues anteriorly as an *intercostal* nerve (Figure 1.2). Each posterior division of the thoracic spinal nerve consists of a medial branch that runs towards the multifidus and longissimus dorsi muscles and innervates the zygapophysial joint, and a lateral branch that supplies the iliocostalis and longissimus muscles and provides small nerves innervating the overlying skin[15,16]. The anterior division of the thoracic spinal nerve runs between the obliquus internus and transversus abdominis muscles and enters the sheath of the rectus abdominis. Along its tract, the intercostal nerve provides lateral and anterior branches innervating the skin.

Anterior cutaneous branches make an almost right angle at the lateral borders of the rectus abdominis muscle. They perforate the muscle through a neurovascular channel and pass through the subcutaneous fascia ending as terminal sensory skin branches. In ACNES, normal function of one or more of these cutaneous branches of thoracic intercostal nerves is disturbed by an unknown event[14]. The exact pathological mechanism is not yet identified but may be related to altered intra- or extra-abdominal pressure. Subsequent compression of

the nerve is possibly due to herniation of the fat pad causing mechanically induced irritation and thereby eliciting severe pain[11,17].

Each thoracic nerve is usually anchored with connective tissue at three specific anatomical sites: (1) at the back where the posterior branches of the thoracic nerve originate, (2) at the flank where the lateral branch originates and (3) at the abdominal wall where the nerve enters the rectus abdominis channel while perforating the rectus muscle (Figure 1.2)[14]. Since the anterior cutaneous branches enter the rectus channel at an almost 90° angle, they are more prone to mechanical irritation compared to lateral or posterior nerve branches. A previously mechanical theory, however, also suggested that nerve compression may cause severe pain at *any* of these three sites, and local nerve entrapment could lead to neuropathic pain similar to ACNES[11]. Two studies in the current thesis will provide insight on specifics of novel entities including the lateral and posterior variant of ACNES, coined by us as Lateral Cutaneous Nerve Entrapment Syndrome (LACNES) and Posterior Cutaneous Nerve Entrapment Syndrome (POCNES).

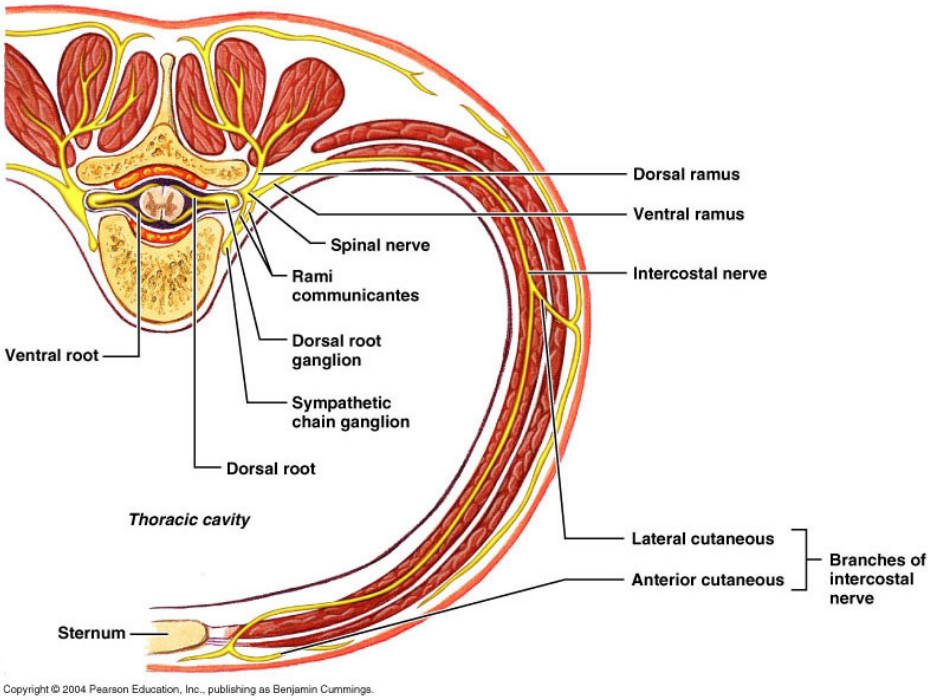

Figure 1.2:

Transverse section of the abdominal wall showing the thoracic spinal nerve dividing into a ventral and dorsal ramus. The ventral ramus proceeds as the intercostal nerve and provides lateral and anterior cutaneous branches[18].

Therapy of ACNES

Several treatment options are currently promoted for ACNES. Systemic drug administration is an important first step in treating chronic pain syndromes[19]. However, just limited effects are usually observed after pharmacological treatment consisting of paracetamol, NSAIDs, or even morphinomimetics. Occasionally, a beneficial effect of neuroleptic agents such as gabapentin, pregabaline or amitriptyline is reported[20,21].

ACNES is associated with a severe and unacceptable level of pain dominating a patient's life. Therefore, the vast majority opts for an interventional technique, including trigger point infiltrations (TPI), neuromodulation [such as transcutaneous electrical nerve stimulation (TENS) or pulsed radiofrequency (PRF)], or surgery[2,11,22-24]. The technique of abdominal wall injection using lidocaine (1%) as a local anesthetic was described by Applegate[11]. After skin disinfection, the point of maximal pain is marked with a pencil. A 21 G 40mm needle is blindly inserted just subfascial to the ventral anterior rectus sheath, and a volume of 5 to 10 mL lidocaine 1% is injected depending on weight and/or local subcutaneous thickness. This procedure may also be guided by ultrasound possibly resulting in a more 'targeted' and accurate approach. Studies have shown that large volumes of anesthetic agents may lead to increased rates of adverse events and may reduce diagnostic specificity[25-27]. Pain relief under ultrasound guidance, however, was not improved compared to a free-hand technique although randomized studies were not performed[28,29]. To minimize the volume of an anesthetic agent, local electrical nerve stimulation under ultrasound guidance such as proposed during PRF may be worthwhile. This technique potentially localizes the affected nerve more adequately and possibly reduces the risk of adverse events[30]. Alternative interventions such as transabdominal plane (TAP) blocks, partial rhizotomy or TENS were of limited success in ACNES patients[31-33].

Pulsed Radiofrequency

Research on minimal invasive treatment options for ACNES such as PRF is exceedingly scarce, but may be explored as suggested in earlier studies[34-36]. PRF can also be deployed as a stand-alone treatment, instead of just localizing the affected nerve. PRF is a relatively new treatment option that was initially adapted as a less destructive approach when compared to conventional Radiofrequency (RF) therapy. Using intermittent administration of high frequency currents, tissue temperatures do not exceed 42°C preventing neuronal damage[37,38]. A number of clinical studies showed a potential as levels of chronic pain in a variety of pain syndromes were significantly reduced[39,40]. High level evidence regarding the efficacy of this treatment in ACNES patients is scarce. Two case reports showed successful outcomes after PRF treatment of the dorsal root ganglion (DRG) resulting in pain reduction and improved quality of life[41,42]. Research further investigating efficacy, safety and long-term effect is lacking.

Surgical interventions

Whenever a conservative treatment regimen fails in ACNES patients, surgical interventions are proposed[43]. Surgical anterior neurectomy is an open procedure exposing the nerve bundle via a 4-6 cm transverse incision. The nerve and all of its branches within a 5-cm radius are coagulated or transected. One study reported a 70% success (defined as >50% pain reduction) at short term follow-up[43]. The long-term efficacy (median 32 months) was 61%[44]. Up to 15% of patients, however, develop recurrent disease, usually after 6 and 12 months. A posterior neurectomy, removing the nerve in a deeper abdominal layer, is associated with up to 70% success rates[24]. Postoperative complication rates of neurectomy procedures are low (<10%) including hematoma/seroma formation or wound infection[24,43,44]. Using a step-up treatment algorithm entailing conventional treatment options such as trigger or tender point injections followed by an anterior neurectomy and a secondary neurectomy in failures or recurrent disease can cure up to 85% of unselected ACNES populations[24].

Although the scientific literature on ACNES has expanded considerably in recent years, a number of aspects are unexplored. A handful of case reports suggested that a lateral and posterior variant of ACNES also existed, but clear clinical descriptions covering these entities or diagnostic and therapeutic protocols are lacking[45-47]. Furthermore, while the merits of a step-up treatment algorithm were established in well-designed randomized controlled trials, little is known of the exact position of surgery within the overall treatment algorithm. Research on new, minimally invasive treatment options such as PRF could be of potential benefit and should be explored in ACNES prior to treatment algorithm incorporation. Lastly, thoroughly investigating characteristics of history and pain allowing for the construction of a set of clear criteria may aid physicians in the diagnostic process.

OBJECTIVE OF THE THESIS

The main objective is to provide evidence on a number of neglected aspects of ACNES including unusual subtypes and to explore alternative treatment options in patients failing a conservative treatment regimen.

Specific aims

1. To report on characteristics of medical history and pain in a large cohort of ACNES patients and to propose diagnostic criteria for ACNES.
2. To evaluate the efficacy of Pulsed Radiofrequency (PRF) for ACNES.
3. To compare efficacy of PRF with a neurectomy in patients with ACNES.
4. To provide a clinical description of novel variants of ACNES (Lateral Cutaneous Nerve Entrapment Syndrome (LACNES), Posterior Cutaneous Nerve Entrapment Syndrome (POCNES).
5. To describe bilateral ACNES and its unique findings at physical examination, pathophysiologic mechanisms and treatment results.

OUTLINE OF THESIS

ACNES is often overlooked as cause of severe chronic abdominal pain (CAP). Much of the current knowledge on this peculiar syndrome is provided by small case series. A general introduction including characteristics of patient history and physical examination in a large case series of ACNES patients is provided in **chapter 2**. Furthermore, treatment results are discussed and a set of major and minor criteria associated with the diagnosis ACNES are proposed.

Most ACNES patients who fail conservative treatment options such as abdominal wall infiltration using an anesthetic agent undergo surgery ('anterior neurectomy'). While this procedure is effective in approximately 70% of the patients, minimal invasive treatment options could be of potential benefit. Pulsed Radiofrequency (PRF) applies an electromagnetic field around the intercostal nerve branch possibly leading to pain relief. Scientific evidence on PRF efficacy in ACNES is scarce. A retrospective case series of 26 ACNES patients is presented in **chapter 3**. Before standardly implementing PRF in the treatment algorithm of ACNES, its efficacy on pain relief should be established in a randomized controlled trial. In **chapter 4,** rationale and outline of a RCT comparing pulsed radiofrequency with anterior neurectomy are presented. **Chapter 5** shows the results of this proposed randomized controlled trial on pain intensity in patients with suspected ACNES who are refractory to other conservative measures including medication or abdominal wall infiltrations.

It was our impression that small subpopulations of patients who were referred for an alleged abdominal wall pain were actually suffering from neuropathic pain, mimicking ACNES, that was located in a different part of the torso. Pain was not located at anterior portions of the abdomen but instead in the flank or at the back. Chronic neuropathic flank pain that resembles ACNES is coined as lateral cutaneous nerve entrapment syndrome (LACNES)**. Chapter 6** contains a case series of patients who were diagnosed and treated with this condition. In **chapter 7** we present a case-report of a patient with a severe type of neuropathic chronic back pain caused by nerve entrapment, dubbed by us as posterior cutaneous nerve entrapment syndrome (POCNES). A case series in **chapter 8** investigates treatment options for this subpopulation including a surgical neurectomy. **Chapter 9** focusses on bilateral presentations of ACNES patients. One of 8 ACNES patients presents with bilateral pain. It is hypothesized that a unilateral peripheral nerve lesion affects contralateral non-lesioned structures and thereby can lead to a 'mirror-image pain' on both sides of the body.

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CHAPTER 2

Characteristics of 1116 consecutive patients diagnosed with anterior cutaneous nerve entrapment syndrome (ACNES)

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ABSTRACT

Background: Chronic abdominal pain in some patients is caused by the anterior cutaneous nerve entrapment syndrome (ACNES). ACNES is a clinical diagnosis as no functional testing or imaging modalities are available up to date.

Objective: The aim of this study is to discuss patient history and subjective findings at physical examination in a large case series to validate a proposed comprehensive set of major and minor diagnostic criteria.

Methods: This study retrospectively analysed prospectively obtained data from consecutive patients who received the diagnosis ACNES during evaluation at the SolviMáx Center of Excellence for Abdominal Wall and Groin Pain, Eindhoven, The Netherlands, between June 1st, 2011 and September 1st, 2016. Questionnaires, standard case forms and digital case files containing characteristics of individuals were used for analysis.

Results: Data of 1116 patients suspected and treated for ACNES consistently showed presence of the four following characteristics: sensory disturbances at the painful abdominal area (78%), a positive Pinch sign (78%), a positive Carnett's sign (87%), and a positive response to a modified rectus sheath block (>50% pain reduction, 81%). The majority of patients is female of young or middle age with a normal BMI reporting complaints that occurred spontaneously in either a sudden or gradual timeframe, developing a severe (NRS 6-8) chronic abdominal pain that was only diagnosed after a substantial doctor's delay.

Conclusions: A combination of typical findings in history and physical examination, combined with a positive modified rectus sheath block may allow for diagnosing ACNES in patients with chronic abdominal pain.

INTRODUCTION

Chronic abdominal pain in some patients is caused by the anterior cutaneous nerve entrapment syndrome (ACNES). Central in this entity is the presence of a chronic severe pain that is invariably present in a circumscript area of the anterior abdomen[1]. The diagnosis is based on the combination of a rather nonspecific history but an characteristic physical examination. As abdominal imaging is frequently normal, this illusive condition is met by skepticism. However, two recent randomized trials investigating the role of diagnostic injections and surgery have contributed to the acceptance of ACNES as a unique entity among a range of abdominal wall pain syndromes[2,3].

In ACNES, pain may be elicited by a change in body position or an exercise provoking the abdominal muscles. Additional clues are the presence of discrete somatosensory abdominal skin disturbances and increased pain when simultaneously tensing the rectus abdominis muscle and palpating the painful area (Carnett's sign). Moreover, a disproportionate sense of pain following squeezing of the skin portion covering the point of maximal pain is often reported (positive Pinch test)[4].

Abdominal pain due to ACNES is easily missed or erroneously judged as pain of visceral origin such as occurring with an irritable bowel syndrome (IBS). One study in a Dutch primary care setting revealed that some 3-4% of chronic abdominal pain patients who were previously classified as having IBS were actually suffering from ACNES[5]. If one extrapolates this percentage for example to the situation in the United States of America, many thousands of ACNES patients are currently misdiagnosed with IBS or functional abdominal complaints.

There are also other data indicating that ACNES is probably more common than previously thought. The ACNES incidence in patients evaluated for acute abdominal pain in an emergency department of a large teaching hospital was approximately 2%[6]. Moreover, ACNES may occur at any age, including children and octogenarians. Physicians of virtually all sorts may be confronted with this condition including gastro-enterologists, gynecologists, pediatricians, pain specialists, surgeons and general practitioners. Once ACNES is considered based on history and physical examination, pain relief following a subfascial rectus sheath block using a local anesthetic agent contributes to the diagnosis[3].

The pathophysiology of ACNES is incompletely understood. Between the 1950s and 70s it was hypothesized that this neuropathic pain syndrome likely occurred due to entrapped end twigs of intercostal nerves[7]. These intercostal nerves find their origin at the 7th to 12th thoracic vertebrae and traverse along the costae to the abdominal wall and innervate the oblique muscles. Nerve endings were thought to be compressed while tunneling through posterior portions of the rectus abdominis muscle, possibly provoked in situations of elevated intra-abdominal pressure occurring for instance during pregnancy or laparoscopic surgery. These end branches are almost purely sensory at the level of the rectus muscle and often less than one millimeter in diameter, precluding proper imaging. However, entrapment is likely just one of more pathophysiological mechanisms, as some 60% of patients reported the absence of any event contributing to the onset of ACNES[8].

Therapeutic options in ACNES are based around the paradigm of entrapment and intercostal nerve irritation. Local abdominal wall injection therapy, pulsed radio frequency treatment and surgical removal of a portion of the strained nerve using an anterior neurectomy are the cornerstones of treatment. However, modalities such as rehabilitation therapy, physical therapy and connective tissue massage are under debate as well as advanced neuromodulation techniques such as spinal cord stimulation[9].

As a tertiary referral center, a surgical subdepartment (SolviMáx) of our hospital is exposed to a large number of patients with chronic abdominal wall and groin pain syndromes. Aim of the present large case series encompassing over thousand ACNES patients who were diagnosed during a 5-year-period is to discuss characteristics and propose a set of major and minor criteria associated with the diagnosis ACNES, with respect to global treatment results in this population. Moreover, mechanisms potentially evoking the syndrome as well as remarkable clues in history and physical examination are discussed.

METHODS

Study design

This study retrospectively analyzed prospectively obtained data from consecutive patients who were referred to the SolviMáx Center of Excellence for Abdominal Wall and Groin Pain, Eindhoven, The Netherlands, between June 1st, 2011 and September 1st, 2016. All were suspected of having ACNES and received treatment. The database search was conducted between August 1st – September 1st 2017. Home questionnaires, outpatient evaluation, standardized case forms and digital case files containing characteristics of individuals were entered in a comprehensive database that was used for analysis. Anonymized coding of data was performed and monitored by two independent investigators (FM&RM). Excluded for analysis were cases in which the diagnosis was doubtful, if no treatment was started, if a follow up appointment was not made or if non-compliance to a first follow-up visit was determined, which is especially important to assess the effect of a possibly given diagnostic block. Data of excluded patients were tabulated (Appendix A). All patients had signed informed consent forms prior to intake allowing for the use of anonymized patient related outcome measures. The study protocol was approved by the medical ethical committee of Máxima Medical Center, Veldhoven, The Netherlands.

Specifics of diagnostic evaluation

Prior to receiving an outpatient invitation, each individual who is presented by a referring party is requested to complete a paper questionnaire including a number of items such as specifics of history, medication use, events possibly provoking the pain, previous and current diagnoses, investigations, imaging and operations, additional comorbidity, duration of symptoms, nature

of the pain sensation and the presence of pseudovisceral complaints such as nausea, bloating, or altered defecation, as well as the previously developed 18-item Chronic Abdominal Wall Pain scale shown in Appendix B[10]. A score <10 points is associated with IBS rather than an abdominal wall pain problem. Once these data are evaluated and deemed possibly consistent with an abdominal wall or groin pain syndrome, patients are invited for an outpatient evaluation. Completion is required for an invitation.

During a 30 minute primary consultation, the history is confirmed as documented in the questionnaire by one of four physicians (three surgeons) who are highly experienced in the evaluation of chronic abdominal wall and groin pain syndromes. Numeric pain rating scores (PI-NRS) reflecting the average pain in the week preceding the consultation are obtained. Specific findings of physical examination that were standardly assessed were skin sensibility surrounding the painful point (hypo- or anaesthetic, hyperaesthetic, hyperalgesic), an increase of pain upon simultaneously flexing the abdominal muscles and digital palpation of the painful point (Carnett's test), a disproportionate increase of pain while slightly pinching the abdominal wall (Pinch test) and the presence of painful points along the ipsilateral costal margin to the flank or paravertebral area. This latter phenomenon is often associated with proximal irradiation of neural hyperactivity.

Specifics of diagnostic rectus sheath block

If a combination of history and physical examination suggests the presence of ACNES, the diagnosis is communicated and a subfascial injection of 5-10 ml of 1% lidocaine depending on the body weight is administered at the maximum tender point using a free hand technique, as previously published[3]. Levels of pain are scored immediately before and ±15 minutes after injection using PI-NRS. Injections are always provided by one of the four attending physicians. A block is deemed positive if a minimal 50% decrease of PI-NRS is reported. Occasionally, this diagnostic test was not performed if patients refused an injection, if previous injections were administered elsewhere, or an allergy for lidocaine was reported.

Treatment algorithm

Based on previous results from our research group, we follow a standard step-up treatment protocol in a new patient. Starting with minimal invasive therapies such as subsequent tender point infiltrations with a local anesthetic and added corticosteroids, or pulsed radio frequency (PRF) treatment of the peripheral nerve or dorsal root ganglion. Success rates of these therapeutic options, defined as >50% pain reduction, range between 30-50%[9]. A portion of patients is dissatisfied with these treatments alone and opt for a neurectomy. Standard follow-up evaluation is 6-8 weeks after the last injection, PRF treatment or neurectomy. Over the years, some patients explored other treatments such as deep tissue massage, rehabilitation therapy, transcutaneous electric nerve stimulation (TENS), etc.

Specifics of a neurectomy

During a neurectomy, terminal nerve branches of the n. intercostales are removed at the point of maximum pain over the rectus muscle. Patients who experience insufficient pain relief after this procedure are eligible for a second operation. During this procedure, the neurovascular bundle is identified and removed at the posterolateral border of the muscle

Statistical analysis

Determinants were analyzed using SPSS 22.0 (IBM, NY, USA) if >85% data was complete. Categorical measures are presented as percentages. Continuous data are presented as mean values (and standard deviation, SD) or median (and range) where appropriate. Analysis of categorical data in subgroups was performed using χ^2 or Fisher's exact test where appropriate. PI-NRS difference was calculated with Wilcoxon signed rank test.

RESULTS

Selection

A total of 3117 patients were referred during the 5-year period of observation. 2996 patients (96%) were evaluated for alleged chronic abdominal wall pain or groin pain after screening of completed questionnaires. Of these, 1217 were coded as having ACNES. The remaining group of patients (n=1779) suffered from a range of abdominal wall and groin pain conditions including inguinal nerve neuropathies such as chronic postherniorrhaphy inguinal pain (CPIP) and postpfannenstiel syndrome. Other diagnoses varied from sportsman's hernias to somatoform disorders. Of the 1217 ACNES patients, 59 were excluded from analysis because the diagnosis ACNES was later rejected or multiple pathologies coincided (e.g. abdominal wall endometriosis and ACNES). Another 42 patients were excluded as outpatient follow up data after the first visit were not available (Appendix A). Therefore, the present study is based on 1116 patients diagnosed and treated for ACNES (Figure 2.1).

Subject characteristics (n = 1116)

Demographics of the 1116 analyzed patients are depicted in Table 2.1. Median age was 42 (range 7-81). Age peaks were observed at the age of 16 and 40. The majority of patients was female (3.6:1). BMI was normal (24±9). In most cases (57%), the pain started spontaneously without any evident cause. However, 28% of patients reported abdominal surgery (either open or laparoscopic) as the mechanism of onset. Incidentally reported etiologies were an accident or a sport's injury (5%), pregnancy (3%) or a flu (3%). A small portion of patients mentioned other triggering events such as IUD placement or a colonoscopy. Two patterns of pain onset were observed, either gradual (42%) or sudden (53%). On average,

pain was severe as mean NRS scores on a characteristic day were 6 (±2) and peaked to 8 (±1). Patients scored on average 14 points (±2) on the CWAP scale, as published by van Assen et al[10].

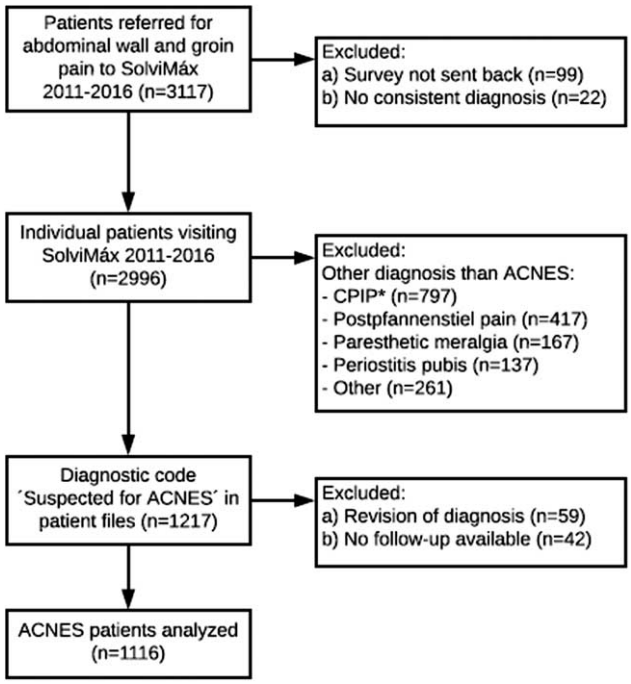

Figure 2.1:

Screening of a 5 year SolviMáx database to identify ACNES patients.

Abbreviations: ACNES = Anterior Cutaneous Nerve Entrapment Syndrome; CPIP = chronic postherniorrhaphy inguinal pain

Patients were mostly referred by general practitioners, surgeons and pain specialists but gastroenterologists, pediatricians and gynecologists were also regular referring specialists. Median doctor's delay was median 18 months. Some patients were diagnosed at the emergency department within days after onset, others already had years of complaints and unsatisfactory diagnostic labels before ACNES was considered by a specialist familiar with the syndrome. Other pain syndromes such as irritable bowel syndrome, fibromyalgia, complex regional pain syndrome and rheumatoid arthritis were present in 17% of the patients.

Pseudovisceral complaints were reported by 47% of patients, predominantly bloating and nausea.

Table 2.1:
Demographics of 1116 ACNES patients.

No of studied patients	(n=1116)
Age*	42 (7-81)
Sex ratio M:F	1:3.6
Height (cm)**	169 (10) cm
Weight (kg)**	73 (17) kg
BMI (kg/m²)**	24 (9)
Etiology (n)	
Spontaneous	57%
Recent abdominal surgery	28%
Accident/sport injury	5%
Pregnancy	3%
After a flu	3%
Other	3%
Gradual vs sudden onset	42% vs 53%
Duration of pain prior to diagnosis (months)*	18 (1 - 120)
Presence of (pseudo) visceral symptoms	47%
Presence other pain syndromes	17%
NRS normal**	6 (2)
NRS peak**	8 (1)
CWAP score**	14 (2)
Referring physician	
1 = General practitioner	40%
2 = Surgeon	22%
3 = Anesthesiologist/pain specialist	11%
4 = Gastrointestinal physician	10%
5 = Pediatrician	5%
6 = Emergency department	4%
7 = Other	7%
Previous treatment elsewhere for ACNES	47%

Abbreviations: NRS = Numeric Rating Scale; BMI = Body Mass Index. CAWP score = Chronic Abdominal Wall Pain score. Data are presented as medians (*) with ranges or means (**) with standard deviations, as appropriate, or percentages.

Findings during physical examination

Pain characteristics are summarized in Table 2.2. The point of maximum pain was often encountered (55%) at the right side of the abdominal wall, lateral or just caudal to the umbilicus in dermatome T10 and T11. Positive symptoms associated with ACNES were local somatosensory disturbances such as hypo- or hypersensitivity and altered cold perception (78%), positive skin pinching (78%) and a positive Carnett's sign (87%). Lateral and paravertebral painful points were present in 16% and 15% of patients, respectively. Some 13% of patients

had bilateral complaints, usually with two painful points in a mirrored distribution in the right and left hemi abdomen.

Fifteen minutes after a diagnostic rectus sheath block, almost half of patients (42%) demonstrated complete remission of pain. Another 39% reported a minimal 50% pain reduction whereas 19% reported less than 50% pain reduction, or no effect at all.

Table 2.2:
Pain characteristics and findings at physical examination in ACNES patients.

Included patients	N = 1116
Abdominal wall dermatome of max. pain location	
T7	3%
T8	9%
T9	13%
T10 (level of umbilicus)	27%
T11	34%
T12	14%
Abdominal wall side of max. pain location	
Right	55%
Left	30%
Bilateral	13%
Presence of local somatosensory disturbances around point of max. pain	78%
Hypoesthesia	48%
Hyperesthesia	20%
Allodynia	5%
Positive Pinch Symptom	78%
Positive Carnett Symptom	87%
Presence of intercostal painful points	16%
Presence of paravertebral painful points	15%
Reaction modified rectus sheath block after 15 minutes:	
Pain free	42%
>50% Pain reduction	39%
<50% Pain reduction	19%

Data are presented as percentages of the entire case series.

Treatment regimens & therapeutic results

Patient flow during the step-up treatment protocol is shown in Figure 2.2. Of 1116 patients, 128 were excluded from conservative treatment because they had received such treatments elsewhere. The majority opted for a neurectomy. Eventually, 984 patients underwent injection therapy or/and PRF, with 316 patients experiencing some >50% pain reduction. Injection therapy success rate was 24%, PRF yielded more success (42%). As 235 patients experienced a long term effect of this conservative treatment, 81 of these 316 patients experienced recurrent symptoms beyond

6 weeks and also opted for a neurectomy. Most patients who experienced <50% pain reduction chose to undergo a neurectomy, but some were hesitant towards surgical treatment and explored additional, non-surgical, treatments.

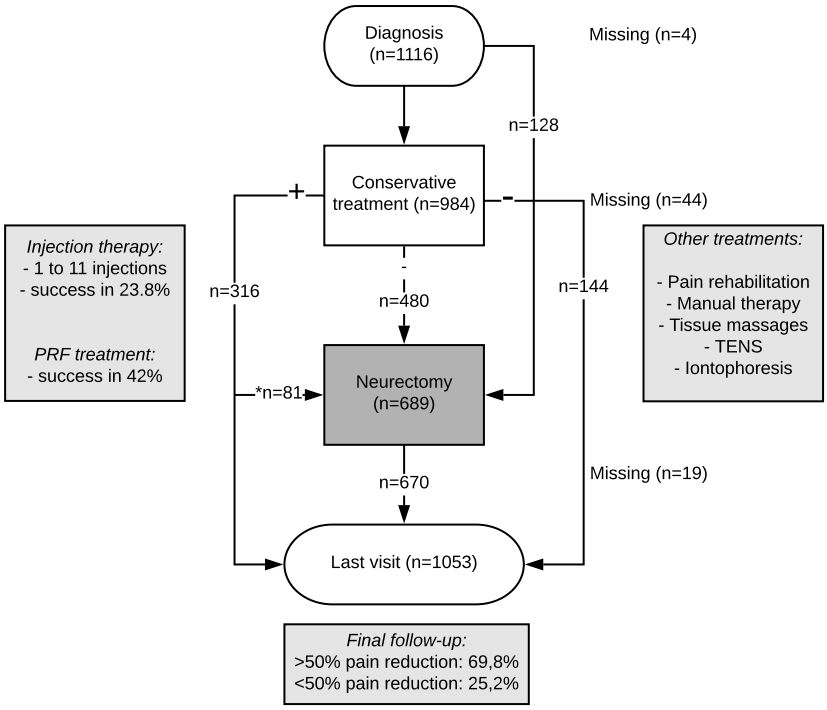

Figure 2.2:

Therapies and success rates in ACNES patients.

Initial operations predominantly consisted of a neurectomy with an anterior approach. In most second operations, a posterior approach was used. A total of 253 patients underwent a second operation. These are patients who experienced insufficient pain reduction after the first procedure or had recurrent symptoms beyond 6 weeks. Tertiary explorations (or more) were reserved for a small group of patients (n=37) after thorough evaluation for the presence of a persistent anatomical substrate.

Follow-up ranged from 12 to 60 months. As treatment efficacy was not the primary focus of this study, no further analyses on outcome issues were performed. Approximately 70% of patients experienced >50% pain reduction at the final visit as recorded in the database, which is consistent with previous reports of our group on (long term) outcome data. One of four patients experienced less than 50% pain reduction at this time point and is thus considered a failure.

DISCUSSION

This study describes the characteristics of the largest case series of ACNES patients to date. Due to our unique position as a tertiary referral center in the Netherlands, a large number of individuals was studied, potentially allowing for an thorough clinical description of the ACNES population. The majority of patients is female of young or middle age with a normal BMI who spontaneously develop a sharp, burning pain, typically in the right lower abdominal quadrant, either suddenly or gradually. The pain is a severe (NRS 6-8 on a 10 point scale) type of chronic abdominal pain that is diagnosed as ACNES after a substantial doctor's delay (median 18 months). These characteristics are largely similar to findings from a smaller case series [8]. The long doctor's delay is likely due to the relative unfamiliarity of physicians with the syndrome, but is surely also caused by possible confusing elements in the patient´s history. Visceral (sometimes called "pseudo" visceral) complaints such as nausea, bloating, increase of complaints after food intake or altered defecation are present in more than half of ACNES patients suggesting some type of gastro-intestinal disease rather than a neuropathic pain syndrome. As such, practically all patients had undergone previous imaging to rule out specific visceral disease. However, the typical history of a chronic pain in a predictable small area of the abdomen is unique for ACNES.

Although the authors recognize the description of such a 'typical' ACNES patient, multiple time points in the diagnostic work-up presented in this study allow for specific forms of bias. Since we are a referral center for alleged ACNES patients, some form of selection bias may be present. Vulnerable patients might not complete questionnaires and could therefore be omitted in the analysis, rendering non-response bias. Three surgeons and one general physician screened the home completed questionnaires and excluded a small number of patients as results seemed more consistent with alternative gastro-intestinal diagnoses. The diagnostic injection technique has been previously evaluated in a placebo-controlled fashion, but it is not impossible placebo responses may have occurred in this large case series. Neurectomies were generally initiated after one or multiple positive injections, although a positive block was not a condition sine qua non. With regard to treatment results, this study only presents routine, relatively short term follow-up that is, however, consistent with previous randomized controlled trials. Rates of success of therapy and recurrences will be presented in future studies.

Nevertheless, analysis of the findings in physical examination provide an essential first step in validation of a proposed syndrome definition. Our previously validated questionnaire to differentiate IBS from abdominal wall pain proves to be a helpful pre-screening tool (appropriate scores in 72% of invited patients, median 14/18 points). During the first visit in our center, the diagnosis ACNES is deemed highly likely if a patient with a localized chronic abdominal pain has at least two of the four following characteristics during physical examination: sensory disturbances at the area of maximal pain (either hypoesthesia, hyperalgesia, altered cold perception), a positive Pinch sign, a positive Carnet's sign, and a positive response to a modified local rectus sheath block (>50% pain reduction). These characteristics are indeed present in

the majority of patients (respectively in 78%, 78%, 87%, and 81%). Lateral (along the ribs) and paravertebral tender points are only present in a small portion of patients.

The results confirm that the key elements in diagnosing ACNES remain a thorough history and physical examination. To relate this to a comprehensive syndrome description, however, a thorough understanding of the pertinent anatomy, pathophysiology, and the electrodiagnostic manifestations of its pathophysiology is required. Electrodiagnostic studies using quantitative sensory testing have been performed for pre- and post-neurectomy assessment, identifying favorable responders[11].

The present description of patient characteristics may provide some clues regarding the pathophysiology of ACNES as well. For example, a large subset of patients developed symptoms after either open abdominal or laparoscopic surgery or during pregnancy and after trauma, suggesting some kind of mechanical etiology. It is not difficult to imagine that the small anterior nerve branches are at risk of being damaged during a skin incision or following insufflation of the abdominal cavity or elongation and traction forces during pregnancy and trauma, respectively[12].

In ACNES patients who spontaneously developed symptoms it might be theorized that intermittent entrapment of the nerve has resulted in sensitization. Due to elevated pressure in the rectus compartment, ischemia and chronic edema of the perineurium and endoneurium may arise, possibly leading to dysfunctional firing of the nerve[13]. After the initial traumatic event, instead of returning to their resting state, pain transmission neurons throughout the CNS gain consequent increased excitability due to synaptic plasticity. There is concomitant glial activation both at the segmental level, in a mirror distribution, and around the strained nerve[14]. This is a dynamic process that often spreads proximally to the site of the original event[15]. These phenomena may explain the relatively large group of patients with a bilateral, very strict symmetrically, mirrored distribution (in the present series some 13%), as it is unlikely that two separate nerves become entrapped at exactly the same anatomical level of the right and left m. recti, although not impossible.

Apart from these mechanical injury and entrapment theories, so called referred pain mechanisms or segmental relations might also play an important role in a substantial portion of ACNES cases[16,17]. Viscero- and somatoafferent (nociceptive) neurons converge at the level of the dorsal root ganglion and as such abnormal activity of an organ (as in transient disease) can be interpreted by the brain as a stimulus originating within the same segment, such as for example the same dermatome or myotome. This might explain why some 47% of patients reported pseudovisceral complaints. Presenting with local sensory disturbances and pain, the underlying cause in these patients might not initially be of primary neuropathic origin, but still originating from a visceral event. This sequence of events has indeed been observed in patients presenting with a (later) proven acute appendicitis[18]. Since various pathophysiological pathways may possibly lead to the clinical manifestation of ACNES, future research should focus on the development of quantitative diagnostic tools and exploring tailor-made treatment options.

CONCLUSIONS

A combination of typical findings in history and physical examination, combined with a positive modified rectus sheath block may allow for diagnosing ACNES in patients with chronic abdominal pain. Physicians should be aware that pseudovisceral symptoms such as nausea, bloating, diminished appetite or altered defecation are also associated with this syndrome and their presence does not exclude this diagnosis. The typical ACNES patient is a young or middle-aged female with severe continuous right-sided lower abdominal pain that developed spontaneously without any evident cause. A subgroup of patients may present themselves with bilateral symptoms or tender points along the trajectory of the intercostal nerve, which could be suggestive for central sensitization of an initial localized neuropathic pain entity. Treatment results in this population are consistent with previous randomized controlled trials.

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APPENDICES

Appendix A.
Demographics of ACNES patients who were excluded from analysis (n=66).

Excluded patients		(n=66)
Age*		47 (8-78)
Sex ratio	M:F	1:3,9
Height (cm)**		171 (8) cm
Weight (kg)**		75 (14) kg
BMI (kg/m²)**		25 (4)
NRS normal**		6 (2)
NRS peak**		8 (1)

Abbreviations: NRS = Numeric Rating Scale; BMI = Body Mass Index. Data are presented as medians (*) with ranges or means (**) with standard deviations, as appropriate, or percentages.

Appendix B.
Chronic Abdominal Wall Pain questionnaire.

For me pain dominates over discomfort	(yes=1, no=0)
Pain is always located on the same spot(s)	(yes=1, no=0)
Pain is located just lateral to the midline of the abdomen	(yes=1, no=0)
The most intense pain can be localized by the tip of one finger	(yes=1, no=0)
I believe the pain is originated just beneath the skin	(yes=1, no=0)
Pain is provoked by daily activities (eg, walking, sitting, cycling, bending)	(yes=1, no=0)
Lying on the affected side aggravates the pain	(yes=1, no=0)
Pushing on the painful spot aggravates the complaints	(yes=1, no=0)
Coughing, sneezing of squeezing aggravates the pain	(yes=1, no=0)
The painful spot feels strange, different or dull	(yes=1, no=0)
I believe the complaints originate from my gastro-intestinal tract	(yes=0, no=1)
Pain exists on different spots all over the abdomen	(yes=0, no=1)
Complaints are somehow related to an altered defecation pattern	(yes=0, no=1)
Stress provokes the complaints	(yes=0, no=1)
I experience bloating or a feeling of gas in the intestines	(yes=0, no=1)
The stool has an abnormal consistency (eg, hard and small, pencil thin, loose, watery)	(yes=0, no=1)
I feel urgent need for bowel movement without producing stool (incomplete defecation)	(yes=0, no=1)

Each of the 18 questions scores 0 or 1 point leading to a total 0-18 point score. A >10 point score is associated with Anterior Cutaneous Nerve Entrapment Syndrome (ACNES) whereas a <10 point score is suggestive of visceral disease including Inflammatory Bowel Syndrome (IBS) (10).

CHAPTER 3

Pulsed radiofrequency as a minimally invasive treatment option in anterior cutaneous nerve entrapment syndrome: A retrospective analysis of 26 patients

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ABSTRACT

Background and aims: Chronic abdominal pain is occasionally due to entrapped intercostal nerve endings (ACNES, abdominal cutaneous nerve entrapment syndrome). If abdominal wall infiltration using an anesthetic agent is unsuccessful, a neurectomy may be considered. Pulsed Radiofrequency (PRF) is a relatively new treatment option for various chronic pain syndromes. Evidence regarding a beneficial effect of this minimally invasive technique in ACNES is lacking. Aim is to assess the effectiveness of PRF treatment in ACNES patients.

Methods: A series of ACNES patients undergoing PRF treatment between January 2014 and December 2015 in two hospitals was retrospectively evaluated. Pain was recorded prior to treatment and after 6 weeks using a numerical rating scale [NRS, 0 (no pain) to 10 (worst possible pain)]. Successful treatment was defined as >50% NRS pain reduction. Patient satisfaction was scored by patient global impression of change (PGIC, 1 = very much worse, to 7 = very much improved).

Results: 26 patients were studied (17 women, median age 47 years, range 18-67 years). After six weeks, mean NRS score had dropped from 6.7 ± 1.2 to 3.8 ± 2.3 ($p<0.001$). A mean 4.9 ± 1.4 PGIC score was reported by then. Short term treatment success (6-8 weeks) was 50% (n=13, 95% CI 29 to 71), while 8% was pain-free on the longer term (median 15 months). Median effect duration was 4 months (range 3-26).

Conclusions: PRF is temporarily effective in half of patients with ACNES. PRF is safe and may be favored in neuropathic pain syndromes as nerve tissue destruction is possibly limited. A randomized controlled trial determining the potential additional role of PRF in the treatment strategy for ACNES is underway.

INTRODUCTION

In chronic abdominal wall pain (CAWP) syndromes, the abdominal wall harbours a focus responsible for generating and maintaining the pain stimulus. CAWP is often caused by the anterior cutaneous nerve entrapment syndrome (ACNES)[1]. In ACNES, terminal branches of thoracic intercostal nerves are thought to be "entrapped" by an hitherto unidentified event[2]. Patients present with a circumscript pain point within the lateral boundaries of the rectus abdominis muscle. Moreover, skin sensation covering this tender point is altered, and often a positive pinch test and a positive Carnett's test (increased local tenderness by tensing the abdominal muscles) are found[3,4]. ACNES incidence rates in an emergency department of a large teaching hospital approximated 2% in patients presenting with acute abdominal pain[5]. Knowledge on this cause for chronic abdominal wall pain is still limited and it therefore remains a diagnostic challenge for general physicians and specialists[1,6].

If patients are diagnosed with this syndrome, a treatment regimen including tender-point injections may be initiated, whereas a neurectomy is only offered to injection therapy refractive patients[7]. This treatment algorithm, based on various RCTs and large case series, is successful in up to 80-90% of a random ACNES population[8]. However, less-invasive procedures may also be of potential benefit in patients with ACNES although solid evidence is currently lacking.

Pulsed Radiofrequency (PRF) is an example of such an alternative, minimally invasive treatment. There are two types of radiofrequency (RF) treatment. RF uses a high-frequency alternating current to create a thermal lesion at the targeted nerve disrupting nociception[9]. Coagulative tissue destruction is accomplished once the probe reaches temperatures up to 80°C[10]. RF treatment has been used in various pain syndromes for over 30 years with encouraging results[11-13]. However, RF may also be associated with risks such as deafferentation pain syndromes and neuritis[10,14,15]. Pulsed radiofrequency (PRF) treatment was designed as a less destructive alternative. PRF uses intermittent administration of high frequency current resulting in tissue temperatures below 42°C and therefore, irreversible neuronal damage is prevented[16,17]. Several clinical studies demonstrated significantly reduced levels of chronic pain in various pain syndromes using PRF[18-22].

Evidence regarding the potential beneficial use of PRF in ACNES is sparse. Two cases reported on PRF treatment of the dorsal root ganglion (DRG) leading to pain reduction and improvement of quality of life in both[23,24]. However, the efficacy of PRF at the level of anterior abdominal wall itself is unknown. Aim of this retrospective case series was to assess the effectiveness of PRF in ACNES patients. Furthermore, unfavourable side effects or complications of PRF treatment were tabulated. If PRF is potentially effective, data may be used for initiating a randomized controlled trial comparing PRF with a neurectomy in patients with injection recalcitrant ACNES.

METHODS

General information

In the past decade, the two senior surgical authors (MS, RR) of Máxima Medical Centre (MMC) in Veldhoven have developed an interest in optimizing the treatment algorithm of patients with ACNES including abdominal injections and operations (neurectomy)[3,7,25]. Pain departments of two neighboring hospitals (Rijnstate Hospital, Arnhem (RHA); Radboud University Medical Center, Nijmegen, UMCN) have experience in using PRF at the rectus abdominis muscle level in patients with ACNES. Patient charts were retrospectively reviewed by the first author. Local ethics committees of the two participating hospitals approved the study protocol and decided that the Medical Research Involving Human Subjects Act (in Dutch: WMO) did not apply to. The present analysis was considered auditing of own results and evaluation of patient-reported outcomes.

Eligibility criteria

Patients with ACNES as determined by pain specialists of RHA and UMCN were eligible for the study if they were >18 years old, if they experienced locoregional abdominal pain for at least 1 month, and if they met the following criteria associated with ACNES[7]:

1. Unilateral constant area of tenderness located in the abdominal area with a small area (a few square cm^2) of maximal intensity situated within the lateral boundaries of the rectus abdominis muscle,
2. Tenderness that was aggravated by abdominal muscle tensing using the Carnett test,
3. A larger area of altered skin sensation such as hypoesthesia, hyperesthesia or altered cool perception covering this maximal pain point, but not necessarily corresponding to a specific complete dermatome
4. Absence of laboratory or imaging abnormalities,

Patients were excluded if they had undergone earlier PRF treatment at the dorsal root ganglion (DRG) or had received previous surgical treatment for ACNES. Furthermore, cognitive impairment, recent intra-abdominal pathology, other chronic pain syndromes or spinal surgical procedure at or between vertebral levels T7-L1 were also considered exclusion criteria.

PRF procedure

Pain specialists of each of the two participating hospitals all had >5 years of experience in using PRF. Once a patient is diagnosed with ACNES, he/she is counselled on the specifics of the PRF. If verbal consent is obtained, the patient is placed supine on a stretcher. The patient is asked to locate the point of maximal pain. This often small area is marked with a pencil and the overlying skin is prepped with chlorhexidine® and draped. Guided ultrasound will then be applied in order to locate the underlying fascia of the rectus abdominis, which should be located around 2-3 cm lateral from the linea alba. Once the location is identified, the skin will be anesthetized with 1% lidocaine.

A straight, sharp RF cannula (SMK Pole 54 mm needle with 5 mm active tip, Cotop International BV, Amsterdam, the Netherlands) is used that is connected to a PRF Generator (G4, Cosman Medical, Burlington, MA, at the UMCN site; NeuroTherm NT1100 machine, Middleton, MA, at the RHA site) is inserted at a 45 degrees angle through the skin and its tip is positioned between the anterior and posterior fascia of the rectus abdominis muscle (Figure 3.1). A closed electrical circuit stimulation is maintained at a 50 Hz frequency to obtain a sensory stimulation threshold. Tingling sensations occurred at less than 0.5 V in all patients and are considered crucial in determining location of the affected nerve[26]. PRF treatment is then applied for 6 min using settings: 45 V, <42 °C, 20 msec, 2 PPS, impedance <500 Ohm), while maintaining the cannula in the very same spot.

Figure 3.1:

Ultrasound-guided placing of the PRF canula at the tender point.

Right side: the canula (red arrow) positioned just between the anterior and posterior fascia of the rectus abdominis muscle.

On a regular basis after completing PRF therapy, a local anesthetic agent such as ropivacaine 1 mL 0.2% combined with 40 mg of methylprednisolone is left into the area of treatment on indication. On indication was defined as patients having discomfort when their recognizable pain was elicited during treatment. Patients were allowed to treat any residual pain after PRF using analgesic medication as before.

Patient evaluation and data accrual

A search using specific treatment codes associated with PRF was performed in both participating hospitals, aimed at identifying patients who had received PRF treatment for ACNES. If a hospital was not using electronic data registration, written data logs were manually searched. If certain aspects of indication or treatment were unclear, the responsible doctor was asked for clarification.

Characteristics such as history, age, sex, body height, weight and pain-related specifics of eligible patients receiving PRF between January 2014 and December 2015 were entered in a separate anonymized database. Pain levels and patient satisfaction were measured before and approximately 6-8 weeks after PRF, according to local treatment protocols. Pain was scored as the average pain level that was experienced at the follow-up visit, using a numerical rating scale [NRS, 0 (no pain) to 10 (worst possible pain)]. Patient satisfaction was recorded using the Patient Global Improvement of Change (PGIC) scale. PGIC is a 7 point scale depicting a patient's rating of overall improvement. Patients judged the current condition as "very much worse" = 1 to "very much improved" = 7[27]. PGIC scores of 6 or 7 were considered as a positive outcome. Patient telephone interviews between February and June, 2016 included questions on present levels of pain, satisfaction and long-term complications. A successful outcome was defined as >50% pain relief (as calculated using the NRS-scale) and a PGIC score of >5.

Data analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21 for Windows. Categorical variables were described as frequencies. Continuous data were tested for normality and are presented as means with standard deviation (±SD) or median values (interquartile range, IQR) as appropriate. Changes in pain scores after or PRF treatment were evaluated using the Wilcoxon signed rank test. Subanalysis was done to compare between treatment with and without the use of corticosteroids. A p-value of <0.05 was considered significant.

RESULTS

Baseline characteristics

Using our defined search strategy, a total of 415 PRF treatment records were identified in both participating hospitals between January 2014 and December 2015 (Figure 3.2). After removing duplicates, 250 unique patients were assessed for eligibility. A total of 223 patients were excluded for reasons as depicted (Figure 3.2). Therefore, twenty-seven patients with ACNES fulfilled all study criteria. One patient was lost to follow-up leading to a 26 patient study population. Prior to PRF, all of these 26 patients had received a (temporarily) successful diagnostic injection (≥50% pain reduction) followed by one or more repetitive analgesic injections. However, this strategy did not result in sufficient long term relief. Baseline characteristics are depicted in Table 3.1. Median age was 47 years (range 18 – 67). Diagnostic delay prior to the diagnosis of ACNES was 23 months (range 3-216).

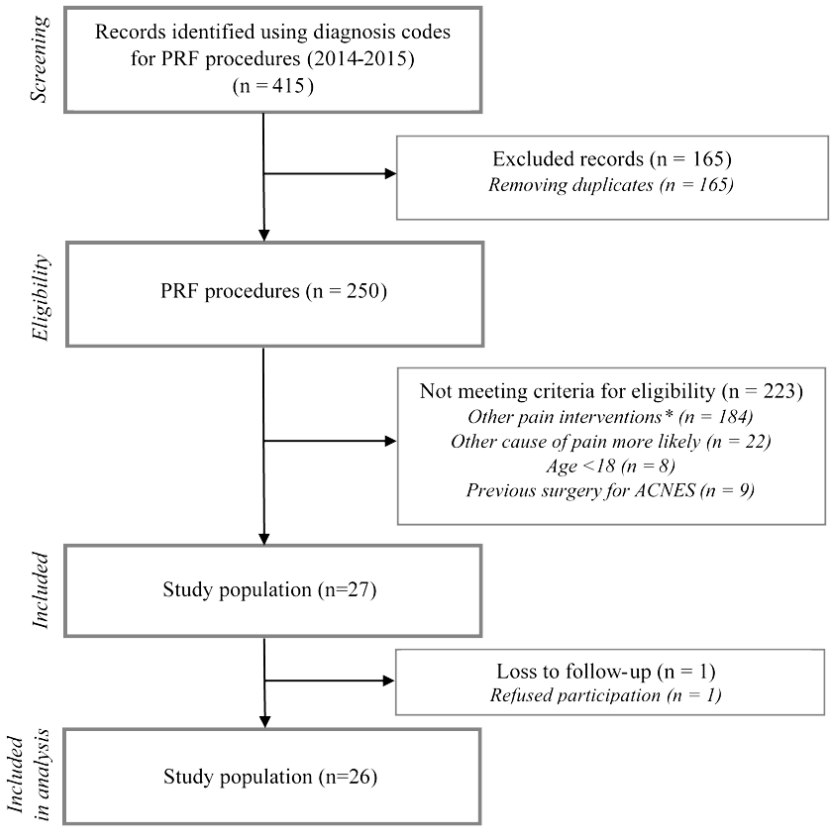


Figure 3.2:

Study Flow Chart

** Other pain interventions included PRF therapy used at the level of the DRG, cryoneuroablation therapy, ultrasound guided trigger-point infiltrations or iontophoresis therapy.*

Table 3.1:
Characteristics of patients receiving PRF for ACNES

	ACNES patients (n = 26)
Age (range)	47 (18 – 67)
Gender, F:M ratio	17 : 9
BMI, kg/m²	25.3 (17.5 – 48.4)
Diagnostic delay, months	23 (3 – 216)
Etiology (n)	
Spontaneous	15
Sport/trauma	1
After flu/infection	1
Previous abdominal surgery	9
Pain (NRS, 0-10)	6.7 (1.2)
Abdominal pain location, n	
Right lower quadrant	10
Right upper quadrant	6
Left lower quadrant	8
Left upper quadrant	2

Data is presented as means with standard deviation (±SD) or median values (range). BMI indicates body mass index.

Short term results (n=26, 6 weeks post PRF)

A mean 6.7 ± 1.2 (95% CI 6.2 to 7.1) NRS score was recorded before PRF treatment. Six weeks later, mean NRS scores had dropped to 3.8 ± 2.3 (95% CI 2.9 to 4.8); $p < 0.001$. At this point, 13 of 26 patients (50% [95% CI 29-71]) considered their outcome as successful (defined as ≥50% pain reduction on NRS scale). All thirteen patients reported a PGIC of >5. A mean 4.9 ± 1.4 PGIC score was identified in the whole study population. The duration of pain before diagnosis did not differ between successful responders and failures (median 24 months, range 6-216 vs median 18 months, range 3-48; p=0.53). No neurological complications or side effects were determined. A subgroup analysis allowed to determine whether use of corticosteroids conferred any treatment effect. Mean differences in pain scores and patient satisfaction after PRF treatment are shown in Table 3.2. A total of 13 patients received corticosteroids after treatment whereas 13 did not for unknown reasons, but most probably because of doctors preference. In this subgroup analysis, changes in NRS scores as well as patient satisfaction were not statistically different among groups (Table 3.2).

Table 3.2:
Subgroup analysis corticosteroids vs no corticosteroids

	Corticosteroids (n = 13)	No use of corticosteroids (n = 13)	Mean difference (95% CI)	P-value
Pain pre treatment (NRS, 0-10)	6.5±1.3	6.9±1.0	0.4 (-0.5 to 1.4)	0.37
Pain post treatment (NRS, 0-10)	3.6±1.5	4.1±2.9	0.5 (-1.4 to 2.3)	0.61
Mean change	2.8±2.0	2.8±2.2	0.0 (-1.7 to 1.7)	0.96
Patient satisfaction (PGIC, 0-7)	5.1±1.3	4.7±1.5	-0.4 (-1.5 to 0.7)	0.48

Data is presented as means with standard deviation (±SD).

Long-term follow-up of (n=26, 15 months)

Long term outcome is depicted in Figure 3.3 (median, 15 months (range 3 – 26, 100% response rate). At that time point, 6 patients reported success (Figure 3.3). Of these 6 successful patients (23%), 2 were pain free on the long term. PRF treatment was effective for a median 4 months (IQR 3-22) (Kaplan-Meier curve, Figure 3.4). A steep loss of analgesic effect was observed anywhere between 2 to 5 months after treatment. Four patients underwent a second procedure resulting in success in all. This pain relief was sustained for approximately 3 to 4 months before its effect again wore off.

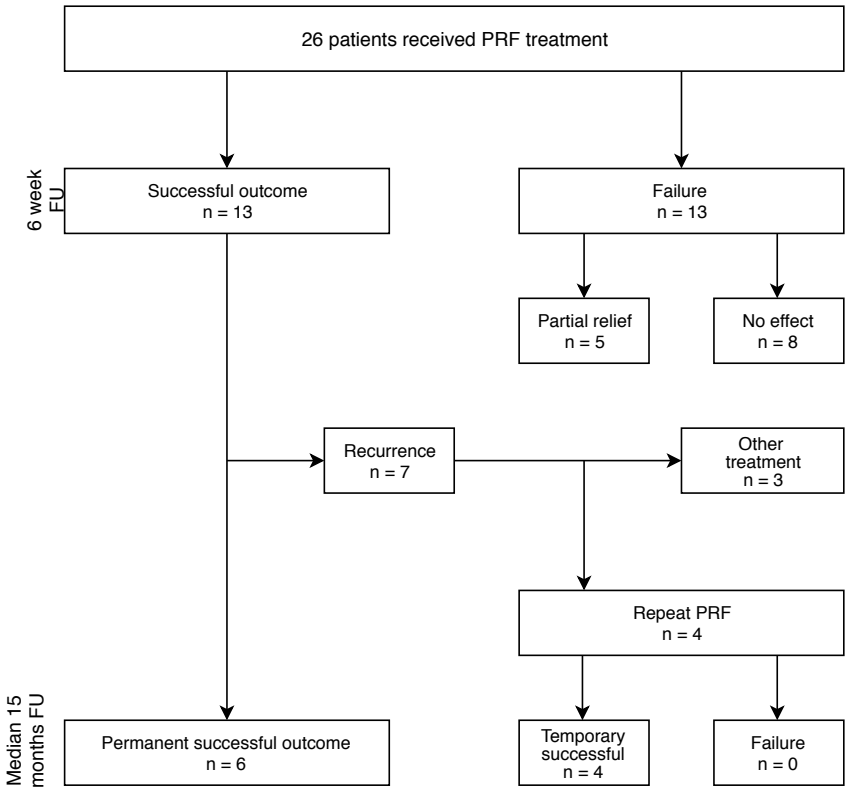
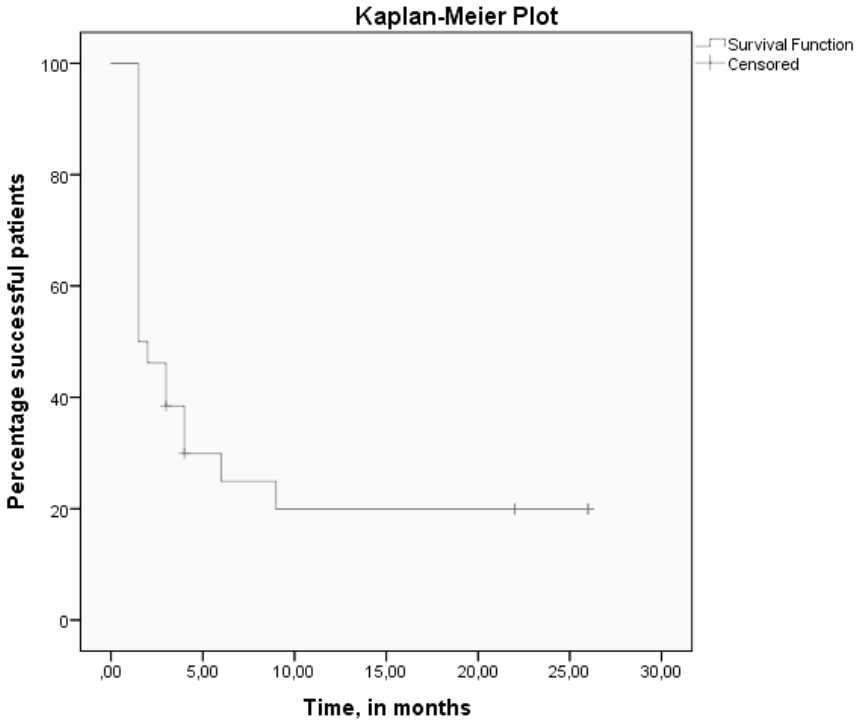


Figure 3.3:

Outcome after PRF treatment in patients with ACNES insufficiently responding to abdominal wall injections

Successful outcome is defined as >50 % reduction of pain during >6 weeks; Temporary successful is defined as >50 % pain reduction for >6 weeks before repeating the procedure; Long term follow-up (FU) is median 15 months (range 3-26).



Numbers at risk					
PRF	26	6	4	4	4

Figure 3.4:

Kaplan-Meier Plot

Time dependent success (>50% pain reduction, Y-axis) of treatment is presented using the Kaplan-Meier method, illustrated as a survival curve.

DISCUSSION

Several studies in ACNES have indicated that surgery such as a neurectomy at the level of the anterior rectus sheath is effective in the majority of patients[7,8]. However, less invasive treatment options may also be beneficial as suggested by two case reports[23,24]. The aim of the present retrospective case series was to address the efficacy and current practice of peripheral PRF therapy in ACNES patients who only temporarily responded positive to abdominal wall infiltrations. The results of the present study demonstrate that PRF provides success (defined as a >50% drop in pain score) in half of the patient population whereas neurological deficits or other adverse side effects were absent. After one year, a quarter of ACNES patients reported an ongoing success, whereas 8% (2 out of 26) was still totally pain free. Therefore, PRF therapy appears of potential benefit as a less invasive alternative to surgical intervention in a small portion of patients with ACNES.

Most researchers would argue that minimally invasive techniques such as PRF (and RF) are mainly considered for short term relief[28]. One review demonstrated that a therapeutic effect of PRF is seldomly detected beyond 6 months[21]. The largest controlled trial evaluating PRF for occipital neuralgia found that potential beneficial effects lasted for over 6 months[29]. Interestingly, repeating PRF treatment may also be explored although pain relief is not necessarily longer after each session[30-32]. The present retrospective data set in a population with ACNES patients suggests that PRF has an identical short term success rate. A Kaplan-Meier analysis illustrates that a beneficial effect diminishes beyond the 5 month time point in most patients**.** Interestingly, untoward side effects of PRF were never reported, even after repetitive administration.

PRF (and RF) treatment are practiced on a large scale for several pain conditions in Dutch pain centers. Moreover, PRF was also used for subgroups of ACNES patients, although high level evidence for this indication is currently absent. We have no clue on what scale this type of treatment is utilized for ACNES in other countries. Evidence favoring PRF treatment in ACNES patients is scarce and limited to two case reports[23,24]. A similar lack of high level data supporting the use of PRF in other chronic pain conditions is observed[33-35]. Since there is no standard treatment protocol and little evidence regarding the use of PRF in ACNES patients, its efficacy should be established with a well-designed randomized controlled trial.

ACNES is hypothesized to be a neuropathic pain syndrome. Neuropathic pain has been defined by the International Association for the Study of Pain (IASP) as pain caused by a (demonstrable) lesion or disease of the somatosensory nervous system[36]. Due to the retrospective nature of this study, the presence of neuropathic pain was not demonstrated by objective tests evaluating somatosensory disturbances such as laser evoked potentials, nerve biopsies, Quantitative Sensory Testing or MRI imaging[37]. We also did not standardly use specific questionnaires focusing on neuropathic pain including DN-4, Pain DETECT or the Neuropathic Pain Syndrome Inventory[37]. However, the mechanical theory proposed by Applegate suggests that terminal parts of cutaneous intercostal nerve branches are ‘entrapped’

in the rectus abdominis muscle and thus leading to an 'entrapment neuropathy'[4]. This theory is strengthened by our observations following a neurectomy procedure, in which these terminal branches are ligated and removed, leading to the disappearance of pain and somatosensory disturbances[3]. Therefore, we are confident that the nature of pain as observed in ACNES is neuropathic.

A remarkable observation in our study was the fact that both participating hospitals regularly administered corticosteroids after PRF. The local administration of these agents may possibly have influenced treatment results, but its role on pain reduction is not clearly understood. A clinically relevant effect of steroids was absent in the present study. It remains debatable whether pain relief is caused by the use of steroids, since 4 out of the 6 successful patients at long-term follow-up never received steroid treatment. In addition, we recently finished a trial in 136 new and previously untreated ACNES patients evaluating the role of adding corticosteroids to abdominal wall tender point lidocaine injections. Interestingly, no beneficial effect of corticosteroids was found.

The present study harbors flaws including its retrospective character whereas a relatively small sample size limits its power and generalizability. Furthermore, a control group eliminating the bias of the placebo effect of a novel treatment option or spontaneous resolution of symptoms is lacking. A previous study showed that a placebo effect of invasive procedures is possibly higher compared to oral medication pills[38]. In addition, some authors suggested that improvement of symptoms that is not obtained in a blind manner is per definition caused by a placebo effect. Therefore, a potential placebo effect cannot be ruled out. However, the results of our study on PRF in ACNES patients must be seen in the proper context. It must be appreciated that most of our patients were referred after a median of over one and a half year of diagnostic delay suggesting that this pain syndrome is still frequently overlooked as a cause of chronic abdominal wall pain[1,39]. It is thus unlikely that the beneficial effect of PRF can be seen solely as placebo effect, since other therapies failed to achieve any success. In addition, a randomized sham-controlled trial showed a beneficial effect for PRF against sham intervention[19]. It must be realized that this study represents the only case series on PRF in ACNES at present providing insight on a "proof of principle" regarding the efficacy of PRF. However, a randomized controlled trial that is currently underway will identify a possible placebo effect.

In conclusion, the present case series is the first to indicate that PRF is a minimally invasive treatment option that may attain a role in the step up treatment algorithm of patients with ACNES. PRF may be favored in neuropathic pain syndromes as nerve tissue destruction is possibly limited whereas side effects are absent. The use of corticosteroids seems to have no additional beneficial value. A randomized controlled trial is warranted to clarify the possible role of PRF and is currently underway at our institute (Netherlands Trial Registration: NTR5131) in order to provide level 1b evidence for the use of PRF in ACNES patients.

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CHAPTER 4

Pulsed radiofrequency or anterior neurectomy for anterior cutaneous nerve entrapment syndrome (ACNES) (PULSE trial): Study protocol of a randomized controlled trial

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Trials 2017; 18:362.

ABSTRACT

Background: Some patients with chronic abdominal pain suffer from an anterior cutaneous nerve entrapment syndrome (ACNES). This somewhat illusive syndrome is thought to be caused by entrapment of end branches of intercostal nerves residing in the abdominal wall. If ACNES is suspected, a local injection of an anesthetic agent may offer relief. If pain is recurrent following multiple injection therapy, an anterior neurectomy entailing removal of the entrapped nerve endings may be considered. After one year, a 70% success rate has been reported. Research on minimally invasive alternative treatments is scarce. Pulsed Radiofrequency (PRF) treatment is a relatively new treatment for chronic pain syndromes. An electromagnetic field is applied around the nerve possibly leading to pain relief. This randomized controlled trial compares the effect of PRF treatment and neurectomy in patients with ACNES.

Methods: Adult ACNES patients having short-lived success following injections are randomized to PRF or neurectomy. At the 8 weeks follow up visit, unsuccessful PRF patients are allowed to cross over to a neurectomy. Primary outcome is pain relief after either therapy. Secondary outcomes include patient satisfaction, quality of life, use of analgesics and unanticipated adverse events. The study is terminated 6 months after receiving the final procedure.

Discussion: Since literature on minimal invasive techniques is lacking, well-designed trials are needed to optimize results of treatment in ACNES. This is the first large randomized controlled proof-of-concept trial comparing two therapy techniques in ACNES patients. The first patient was included in October, 2015. Expected trial deadline is December 2017. If effective, PRF may be incorporated into the ACNES treatment algorithm thus minimizing the number of patients requiring surgery.

Trial Registration: The protocol (protocol number NL53171.015.15) is approved by the Medical Ethics Committee of Máxima Medical Centre, Veldhoven, the Netherlands. The study protocol is registered at www.trialregister.nl (NTR registration number: 5131), date of registration 15th of April, 2015.

INTRODUCTION

Background & objectives

Chronic abdominal pain originating in the abdominal wall is termed chronic abdominal wall pain (CAWP). A CAWP syndrome may be caused by the anterior cutaneous nerve entrapment syndrome (ACNES). At present, ACNES is still often neglected as a possible cause of abdominal pain and discomfort and a frequently overlooked diagnosis[1,2]. An exact pathophysiological explanation of the syndrome is currently lacking but may be related to alterations in abdominal wall neuroanatomy.

The abdominal wall is sensory innervated by anterior and lateral cutaneous branches of anterior rami of thoracic intercostal nerves (7^{th}-12^{th})[3]. In ACNES, normal function of one or more cutaneous branches of thoracic intercostal nerves is disturbed by a hitherto unidentified event[3]. If ACNES is suspected, current treatment options include analgesics, sub-fascial injections of a local anesthetic (whether or not combined with an long acting corticosteroid), transcutaneous electrical nerve stimulation (TENS) and surgical interventions such as anterior and posterior neurectomy. Injection therapy is effective in one third of patients on the long term[4]. A neurectomy is considered in the remaining two-thirds with a reported 70% success rate[5].

Although neurectomy is effective in most patients, a less-invasive procedure may be of potential benefit. Pulsed Radiofrequency (PRF) is a relatively minimally invasive treatment that was initially designed as a less destructive approach when compared to Radiofrequency (RF) therapy. Using intermittent administration of high frequency currents, tissue temperatures do not exceed 42°C preventing neuronal damage[6,7]. A number of clinical studies showed a potential as levels of chronic pain in a variety of pain syndromes were significantly reduced[8,9]. Evidence regarding the use of PRF in ACNES is limited to two case reports on PRF treatment of the dorsal root ganglion (DRG) resulting in pain reduction and improved quality of life[10,11].

Objective of the present paper is to discuss a randomized trial comparing PRF with neurectomy as treatment options in ACNES. Neurectomy is nowadays considered gold standard but less invasive methods may potentially be of benefit.

METHODS

Trial design

This prospective, multicentre, non-blinded, proof-of-concept, randomized trial (with a one way optional crossover at 8 weeks) is performed in the SolviMáx Center of Expertise for ACNES and Center of Excellence for Abdominal Wall and Groin Pain and Maasziekenhuis Pantein, Boxmeer, the Netherlands. SolviMáx is a subdivision of the surgical department of Máxima Medical Center (MMC), a teaching hospital situated in the southern part of The Netherlands. The Dutch Ministry of Health, Welfare and Sport has certified SolviMáx as Center of Expertise for ACNES. The trial will be based on a clinical proof-of-concept design in order to investigate a potential difference in pain relief following either PRF treatment or an anterior neurectomy in ACNES. Furthermore, it is designed to attain more knowledge on the use of PRF on peripheral nerves and to detect possible side effects.

The present trial follows guidelines of the declaration of Helsinki (version October 19th, 2013). The protocol (protocol number NL53171.015.15) is approved by the Medical Ethics Committee of MMC. The study protocol (version 1) is registered at www.trialregister.nl (NTR registration number: 5131, date of registration 15th of April, 2015). The present paper is written according to the SPIRIT 2013 statement for reporting a clinical trial protocol[12]. The SPIRIT checklist is provided as an additional file.

Participants

Patient enrolment started in October, 2015. Patients are identified at the two hospital facilities. Criteria for the diagnosis ACNES are **(1)** a constant site of tenderness that is superficially located covering a fingertip small point of maximal pain at the lateral border of the rectus abdominis muscle, **(2)** a somewhat larger area of altered skin sensation covering this tender point, and **(3)** tenderness increases by abdominal muscle tensing using the Carnett's test[13,14]. Only adult patients (>18 year old) diagnosed with unilateral ACNES and having temporarily success on an injection regimen will be invited for participation. In ACNES, a treatment regimen consists of a local abdominal wall infiltration using 5-10mL of Lidocaine as described in our earlier studies[4,15]. Temporarily is defined as having >50% pain reduction for at least 1 week after such a local infiltration although symptoms recur afterwards (refractory ACNES). Sixty-six patients (male or female) will be enrolled in the trial. Patients are not eligible if pain is caused by surgical scar-related pain syndromes (i.e. point of maximum pain is located at the site of a surgical scar) or due to recent intra-abdominal pathology. Presence of other chronic pain syndromes including fibromyalgia, dystrophy, chronic low back pain, impaired communication, a previous spinal surgical procedure at or between vertebral levels T7-L1 are also exclusion criteria. A full list of inclusion and exclusion criteria is given in Table 4.1. Once eligibility is determined, patients are counseled on the specifics of the study and are given a number of days prior to providing consent.

Table 4.1:
Subject Inclusion and Exclusion Criteria.

Inclusion criteria	Exclusion criteria
· Patient is diagnosed with unilateral ACNES · Eligible for neurectomy (i.e. having temporarily success on injection therapy). · Patient > 18 years old · Patient is able to provide written informed consent · Patient is willing to participate in the follow-up schedule and protocol	· Patient has surgical scar-related pain syndromes · Patient has recent intra-abdominal pathology. · Patient has other chronic pain syndromes (such as fibromyalgia, dystrophy, chronic low back pain · Patient has other neuropathic diseases · Patient has impaired communication · Patient has participated in another clinical investigation within 30 days · Patient has had a spinal surgical procedure at or between vertebral levels T7-L1 · Patient has been diagnosed with cancer in the past 2 years, except for skin malignancies · Female patient of childbearing potential is pregnant/nursing or plans to become pregnant during the course of the trial · Significant anatomic deformity (either congenital or acquired) · Language barrier · Allergy to local anesthetics

Interventions

PRF-arm

Patients will be randomized to one arm of treatment, either PRF or an anterior neurectomy. Patients assigned to the PRF arm will visit departments of pain management of both hospitals for PRF treatment. While being supine, a maximal point of pain is determined by asking and by a physical examination. In ACNES, there is characteristically a small (<2cm^2) constant site of anterior abdominal tenderness. Following marking, the skin is prepped with betadine and draped. Ultrasound (US) is used to locate the anterior fascia of the rectus abdominis muscle. The skin is locally anesthetized using 1% Lidocaine. A straight, sharp RF cannula (SMK Pole needle 54 mm with 5 mm active tip, Cotop International BV, Amsterdam, the Netherlands) is inserted with an approximately 45 degrees angle through the skin (Figure 4.1). The tip of the cannula is then positioned between the anterior and posterior fascia of the rectus abdominis muscle. Electrical impedance is checked confirming a normal, closed electrical circuit. Subsequently, the sensation testing mode (50 Hz, 0.3 - 0.5 V) is started. As the nerve is often not visible using US, this very step is crucial for nerve localization. Sensations such as paresthesia, numbness or prickly-like sensations should occur at less than 0.5 Volts if the needle's position is correct[16]. The cannula is subsequently

connected to the PRF Generator (G4, Cosman Medical, Massachusetts, United States) using the following settings: 45 Volt, <42 Degrees C, 20 mSec and 2 Hz. Treatment is applied for 6 min.

Figure 4.1:

Ultrasound-guided placing of the PRF cannula at the tender point.

Right side: the cannula (red arrow) is positioned just between the anterior and posterior fascia of the rectus abdominis muscle.

Neurectomy arm

Patients assigned to the neurectomy arm will be operated in a day care setting. The area of maximal pain is identified and marked. Once general anesthesia is administered, the anterior sheath of the rectus abdominal muscle is exposed via a ±5 cm transverse skin incision. The neurovascular bundle penetrating into the subcutaneous fat through the pre-existent fascial foramen is identified (Figure 4.2). The fascia is widened and the bundle as all its branches within a 5 cm radius are ligated and removed. Accompanying vascular structures are also ligated or coagulated. The sheath as well as the remainder of the wound are closed in layers using absorbable suturing material.

Medication

Escape medication as currently used for pain reduction is allowed to continue during the entire study period. In daily clinical practice, patients having undergone a neurectomy are always allowed to take analgesics in the postoperative period. Both groups are allowed to take medications at their own need whereas quantities are tabulated.

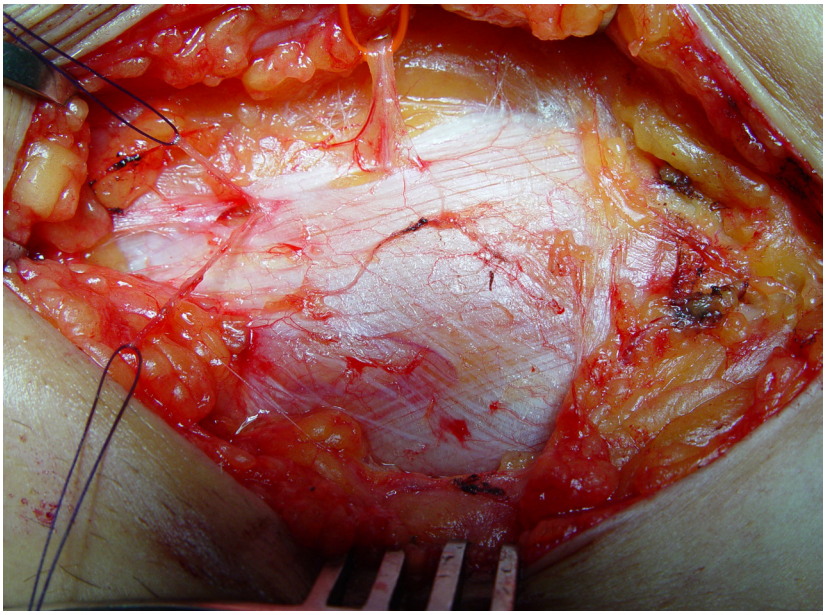

Figure 4.2:

Intraoperative view of a neurovascular bundle (loop) and a nearby branch (loop) perforating the fascial foramina of the anterior sheath of the abdominal rectus muscle.

Outcomes

Primary objective is to compare the effect of PRF with a neurectomy in terms of pain relief at the 8 weeks follow up. Outcome is measured using the Numeric Pain Rating Scale (NPRS, 0 = no pain and 10 = excruciating). Pain is measured at $t_{0,}$ before intervention and 8 weeks after allowing to determine the short-term efficacy (t_1) (Figure 4.3). Long-term efficacy is measured at 6 months follow-up (t_2). Success is defined as >50% NPRS pain reduction following intervention. Secondary outcomes include the effect of PRF or neurectomy on quality of life, disability, neuropathic characteristics, medication usage and satisfaction. The Short Form Health Survey-12 questionnaire (SF-12) is used for measuring the quality of life and interference of pain[17]. Patient disability will be measured with the Pain Disability Index (PDI) and Brief Pain Inventory (BPI)[18,19]. The Douleur Neuropathiqué (DN4) is used in order to discriminate between neuropathic and non-neuropathic pain[20]. Medication usage prior and after treatment will be recorded using WHO pain steps. Patient satisfaction is recorded using the Patient Global Impression of Change (PGIC, 1 very much worse to 7 very much improved) and Verbal Rating Scales methodology (VRS, 1 = I am very satisfied and 5 = Pain is worse after treatment)[4,21].

All adverse events reported spontaneously by the patient or observed by the investigator or his staff will be recorded.

	STUDY PERIOD				
	Enrolment	**Allocation**	**Post-allocation**		**Close-out**
TIMEPOINT	***Pre-intervention***	**0**	***8 wk***	***8 wk crossover***	***6 mo***
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Pulsed Radiofrequency		X	X		X
Neurectomy		X	X		X
Cross-over group				X	X
ASSESSMENTS:					
Age	X				
Gender	X				
Body Mass Index	X				
Pain Measurement (NPRS)	X		X	X	X
Quality of Life (SF-12)	X		X	X	X
Functional Assessment (BPI)	X		X	X	X
Douleur Neuropathique (DN4)	X		X	X	X
Patient Satisfaction (PGIC)			X	X	X
Patient Satisfaction (VRS)			X	X	X
Pain disability (PDI)	X		X	X	X
Crossover decision			+		
Complications			+	+	+

Figure 4.3:

Content for the schedule of enrolment, interventions, and assessments, according to the SPIRIT Statements [12].

Data handling

The investigators and co-investigators will make every reasonable effort to protect the confidentiality of the patients participating in the trial. Patients will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. An unique identification code will be assigned to each patient participating in this trial. Information about the code will be kept in a secure location. Data storage will reside at the co-ordinating site Máxima Medical Centre in locked offices. Sites will retain data collected for a minimum of 15 years. All electronic data will be password-protected on computers stored in locked offices. Access to patient information will be limited to trial personnel only.

Sample size

Sample size estimation is based on a 'responder' analysis, as recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group recommendations[21]. Effect sizes were estimated on the basis of published literature. Neurectomy is considered successful in 70%[13,22-25]. Regarding a potential efficacy of PRF treatment, a mean effect size was estimated at 30%. There is no available literature apart from two case reports on the use of PRF in ACNES patients. The targeted effect size is a difference in proportion responding to treatment (neurectomy vs. PRF) of 40%; i.e., 70% responding in neurectomy group vs. 30% in the PRF group. Using G*Power 3.1.7 software, 80% power, and a two-tailed alpha of 5%, 58 participants are needed to demonstrate a potential effect of either type of treatment on pain relief. With an allowance for attrition of 10% in both arms at 6-month follow-up, we will aim to recruit a total of 66 patients.

Randomization

After enrolment and completing the baseline questionnaires, patients are randomly assigned (1:1 - PRF : neurectomy) to one of two treatment groups following a computer-generated list of random numbers by blocks of 8. Randomization is stratified by treatment site location (Boxmeer or Veldhoven). The allocation sequence is concealed from the enrolling researcher and assessing participants in sequentially numbered, opaque, and sealed envelopes, prepared by a secretary with no involvement in the trial. One central co-ordinating investigator (RM) is responsible for enrolling patients and the only investigator allowed to inform the independent secretary of newly enrolled patients.

Blinding

Blinding of patients, surgeons and pain specialists is not possible due to the characteristics of both treatments (minimal invasive treatment without general anesthesia vs invasive treatment with the use of general anesthesia).

Statistical Methods

All analyses are performed using the Statistical Package for the Social Sciences (SPSS) version 21 for Windows. Categorical variables are described as frequencies. Continuous data are tested for normality and are presented as means with standard deviation (±SD) or median values (range) as appropriate. The primary outcome measure is pain relief using NPRS as compared to the pre-intervention pain levels (t_0). Data of the PRF and neurectomy group will be compared using the student t-test or Wilcoxon signed ranks test, as appropriate. Secondary outcomes will be compared between groups at various time points (baseline, 8 weeks follow-up and 6 months follow-up). They will be compared to pre-intervention values using student-t test or Wilcoxon signed rank test as appropriate. A p-value of <0.05 is considered significant. Analysis of data will be done as randomized (the intention-to-treat analysis), and secondary 'as-treated'.

Recruitment

Potential patients are identified by doctors who are working in abdominal pain clinics at the SolviMáx or the Maasziekenhuis Pantein and are screened for eligibility. Patients are then informed on purpose, nature and duration of the trial. Following consultation, potential participants are allowed fourteen days for consideration. If a patient subsequently consents, he or she is then randomized by the principal investigator. Patients are allowed to withdraw their consent at any given time during the study period.

DISCUSSION

Anterior cutaneous nerve entrapment syndrome (ACNES) is caused by entrapment of end branches of intercostal nerves that are residing in the abdominal wall. Patients suffer from severe abdominal pain that is often not recognized as most doctors are focused, when confronted with abdominal pain, on a visceral source of the pain [1,2]. The diagnosis of ACNES is suggested by a specific combination of the patient's history (chronic pain) and physical examination (circumscript pain localization, positive pinch, Carnett's test and abnormal sensibility) and the absence of objective abnormalities in either laboratory or imaging techniques suggesting possible visceral causes [4]. Once patients are diagnosed with ACNES, a treatment regimen including tender point injections is subsequently offered [4]. If the pain is recalcitrant, a neurectomy is considered. This treatment algorithm is successful in up to 90 % of patients [5]. Research on minimal invasive treatment options is exceedingly scarce but may be explored as suggested [26-28]. Two case reports recently attracted attention to PRF treatment of the dorsal root ganglion (DRG) as a potential alternative approach in ACNES resulting in pain reduction and improvement of quality of life [10,11]. The present study is the first randomized trial comparing PRF and neurectomy in ACNES patients. Results of this proof-of-concept trial may determine if PRF offers an effective treatment option for ACNES.

PRF treatment was initially designed as a less destructive alternative of RF therapy. The technique is based on intermittent administration of high frequency current resulting in tissue temperatures below 42°C preventing neuronal damage [6,7]. Initial studies were promising reporting significantly reduced levels of chronic pain in a variety of syndromes [8,9]. However, evidence on its use on peripheral nerves is scarce. In the present era of evidence-based medicine, well designed proof-of-concept trials are required prior to widespread introduction. PRF is an example of a popular treatment tool for several chronic pain conditions although scientific evidence is rather limited [29-31]. The effect of PRF may depend on type of pain syndrome. Reports on PRF in cervical radicular pain and lumbosacral radicular suggested major pain relief for more than 3 months providing level 1B+ and 2C+ evidence, respectively [8,9]. However, the use of PRF in other pain entities such as lumbar zygapophyseal joint pain and trigeminal neuralgia was found to be less effective than conventional RF [32,33]. Therefore, there is a need

for high level evidence studies confirming the possible beneficial effects of PRF treatment in specified pain syndromes.

A potential limitation of the present study is its non-blinded design. However, blinding patients and/or physicians in the present design is practically impossible.

In conclusion, this randomized controlled proof-of-concept trial will investigate the possible efficacy of PRF treatment as a minimally invasive treatment in ACNES patients. If effective, patients could benefit from its less invasive character whereas the need for surgery is minimized. High level evidence on the use of PRF treatment on peripheral nerve pain syndromes will be increased. The first study results are expected towards the end of 2017 and will be communicated via a publication.

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CHAPTER 5

A randomized controlled trial to evaluate the effect of pulsed radiofrequency as a treatment for anterior cutaneous nerve entrapment syndrome in comparison to anterior neurectomy

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ABSTRACT

Background: Chronic abdominal pain can be due to entrapped intercostal nerves (anterior cutaneous nerve entrapment syndrome, ACNES). If abdominal wall infiltration using an anesthetic agent is unsuccessful, a neurectomy may be considered. Pulsed Radiofrequency (PRF) applies an electromagnetic field around a nerve to induce pain relief. Only limited retrospective evidence suggests that PRF is effective in ACNES.

Methods: A multicenter, randomized, non-blinded, controlled proof-of-concept trial was performed in 66 patients. All patients were scheduled for a neurectomy procedure. Thirty-three patients were randomized to first receive a 6-min cycle of PRF treatment, while the other 33 were allocated to an immediate neurectomy procedure. Pain was recorded using a numerical rating scale [NRS, 0 (no pain) to 10 (worst possible)]. Successful treatment was defined as >50% pain reduction. If PRF treatment was unsuccessful patients were allowed to cross over to a neurectomy after 8 weeks.

Results: The neurectomy group showed a greater pain reduction at 8 weeks follow-up (mean change from baseline -2.8 [95% confidence interval -3.9 to -1.7] vs -1.5 [95% confidence interval -2.3 to -0.6]; P=0.045), than the PRF group. Treatment success was reached in 38% (12/32) of the PRF group and 61% (17/28) of the neurectomy group (P=0.073). Thirteen patients were withdrawn from their scheduled surgery. Adverse events were comparable between treatments.

Conclusions: Although the primary outcome was not significantly different between treatments, neurectomy tends to provide greater and longer lasting pain relief than PRF, in patients suffering from ACNES. However, PRF appears to be an effective and minimally invasive treatment option and may therefore be considered in patients who failed conservative treatment options before proceeding to a neurectomy procedure.

Clinical Trial Registration: NTR5131 (http://www.trialregister.nl).

INTRODUCTION

Chronic abdominal wall pain (CAWP) can be caused by the anterior cutaneous nerve entrapment syndrome (ACNES). The abdominal wall is sensory innervated by anterior and lateral cutaneous branches of anterior rami of thoracic intercostal nerves (7^{th}-12^{th})[1]. ACNES is a condition in which some cutaneous branches of intercostal nerves are entrapped by a hitherto unidentified event, leading to local abdominal pain[1]. ACNES incidence rates in an emergency department of a large teaching hospital approximated 2% in patients presenting with acute abdominal pain[2]. However, ACNES is still often neglected as a possible cause of abdominal pain and discomfort[3,4].

Once the diagnosis of ACNES is established, a treatment regimen of abdominal wall injections is initiated[5]. If abdominal wall infiltration using an anesthetic agent is unsuccessful, a neurectomy may be considered[5-8]. About 70% of patients became pain free after a neurectomy, and remained free of discomfort at a long-term follow-up evaluation[9-11]. Whereas neurectomy is an effective form of treatment in most, a less-invasive procedure could be of potential benefit. Pulsed Radiofrequency (PRF) is an alternative, minimally invasive treatment that recently gained substantial interest as a possible treatment for neuropathic pain[12]. It uses intermittent administration of high frequency current resulting in temperatures that do not exceed 42°C and therefore, irreversible neuronal damage is prevented[13,14]. Its efficacy for neuropathic pain was shown in a number of clinical studies as levels of chronic pain in a variety of pain syndromes were significantly reduced[15-18].

In recent literature, only two case reports suggested that PRF at the *dorsal root ganglion* (DRG) was successful (eg. reduction of pain and improving quality of life)[19,20]. Recently, a retrospective case series of 26 ACNES patients found that PRF was effective in half of the patients[21]. These encouraging results resulted in the execution of the present randomized controlled trial comparing PRF treatment with an anterior neurectomy. Although we do not assume that PRF is superior to neurectomy, a randomized, controlled design allowed for a controlled setting reducing selection bias. It is hypothesized that a substantial portion of ACNES patients benefitted from this minimally invasive form of treatment.

METHODS

This multicenter, non-blinded, randomized controlled trial comparing PRF to anterior neurectomy was conducted at Máxima Medical Center (MMC), Veldhoven and the Maasziekenhuis Pantein, Boxmeer in the southeastern part of The Netherlands between October 2015 and June 2017. The institutional Ethics Review Board of each of the participating centers approved this study and all patients signed an informed consent form (reference number NL53171.015.15). The study was registered at www.trialregister.nl (NTR identification number 5131). The complete study protocol has been published previously [22]. The present paper was written according to the CONSORT 2010 statement for reporting randomized trials [23].

The study was performed in 2 teaching hospitals, of which one (MMC) is a tertiary referral center for patients with alleged abdominal wall pain. Inclusion criteria were age ≥18 years; a diagnosis of an unilateral ACNES according to criteria previously described by Boelens et al[9]; a duration of pain before diagnosis of ≥3 months and temporary success to an abdominal wall injection regimen using 2-5mL of lidocaine 1%. Exclusion criteria were bilateral ACNES; surgical scar-related pain syndromes; recent intra-abdominal pathology; other chronic pain syndromes (such as fibromyalgia); previous neurectomy; previous PRF treatment (at the DRG or peripheral) or nerve blocks for ACNES; spinal surgery at or between vertebral levels T7-L1; pregnancy; or impaired communication. Prior to screening for eligibility, all patients had received an abdominal wall injection regimen. Specifics of the injections were as follows. Patients were placed in the supine position and the point of maximal pain was marked followed by a subfascial injection (of the rectus abdominis muscle) of 2-5mL of 1% lidocaine using a 21 G 40 mm needle. The exact needle depth and amount of administered anesthetic agent was based on the presumed weight of patients and/or the estimated thickness of subcutis covering the tender point. If a >50% pain reduction was observed after a 15- to 20-minute observation period, the abdominal wall infiltration was considered successful, although symptoms may recur afterwards (refractory ACNES)[8].

Sixty-six participants were assigned to one of two treatment groups in a 1:1 ratio. All patients failed conservative treatment (compromising analgesics and an abdominal wall injection regimen) and consented to the next step of our treatment algorithm: a neurectomy procedure. As a consequence, all patients were counselled and scheduled for this surgical exploration. At this time point, patients were approached for study participation. After providing informed consent, they were randomized to either first receive PRF treatment or to the scheduled neurectomy procedure. Since waiting time for surgery in both hospitals was about 8 to 10 weeks, patients would receive PRF treatment within this time window, before cross over to neurectomy was allowed to provide best medical treatment. Enrollment was performed by one central coordinating investigator (RM). Randomization was stratified by treatment site location (Boxmeer or Veldhoven) using a computer-generated list of random numbers by blocks

of 8. The allocation sequence was concealed from the coordinating investigator and assessing participants in sequentially numbered, opaque, and sealed envelopes, prepared by a secretary with no involvement in the trial. Blinding of patients, surgeons and pain specialists was not possible due to the nature of both treatments.

Treatment specifics

PRF-arm

All procedures were performed by highly experienced pain specialists (> 100 PRF-procedures) with the patient in supine position. The area of maximal pain was identified by asking patient combined with a meticulous physical examination. ACNES is characterized by a small (<2cm^2) constant site of anterior abdominal tenderness. Following skin marking, the skin was prepped with betadine and draped. Ultrasound (US) was used to locate the anterior fascia of the rectus abdominis muscle. The skin was locally anesthetized using 1% Lidocaine. A straight, sharp RF cannula (SMK Pole needle 54 mm with 5 mm active tip, Cotop International BV, Amsterdam, the Netherlands) was inserted with an approximately 45 degrees angle through the skin (Figure 5.1). The tip of the cannula was then positioned between the anterior and posterior fascia of the rectus abdominis muscle. Electrical impedance was checked to confirm a normal, closed electrical circuit. Subsequently, the electrical stimulation was performed (50 Hz, 0.3 - 0.5 V). As the nerve is often not visible using US, this very step is crucial for nerve localization. Sensations such as paresthesia, numbness or prickly-like sensations should occur at less than 0.5 Volts if the needle's position is correct and recognized by the patient as being within the correct ACNES region.[24] If those terms were not reached, needle placement was adjusted and electrical stimulation was repeated. If the correct needle position was attained, the cannula was subsequently connected to the PRF Generator (G4, Cosman Medical, Burlington, MA), and treatment was applied for 6 min using the following settings: 45 Volt, maximal temperature of 42°C, 20 ms pulses per second, 2 Hz frequency and impedance <500 Ω. As recorded in the standardized treatment protocol, no additional local anesthetic agent nor corticosteroids were left into the area of treatment.

Neurectomy arm

Patients assigned to the neurectomy arm were operated in a day care setting by one of three surgeons with ample experience (> 100 operations) in anterior neurectomies for ACNES. The area of maximal pain was identified and marked. Once general anesthesia was administered, the anterior sheath of the rectus abdominal muscle was exposed via a 4-5 cm transverse skin incision. Neurovascular bundles penetrating into the subcutaneous fat through the pre-existent fascial foramina were identified (Figure 5.2). The fascia was widened and the bundle as all its branches within a 5 cm radius were ligated or coagulated as previously published.[9] Accompanying vascular structures were also ligated or coagulated. The sheath as well as the remainder of the wound were closed in layers using absorbable suturing material.

Figure 5.1:

Ultrasound-guided placing of the PRF cannula at the tender point in an ACNES patient.

Right side: the cannula (red arrow) is positioned just between the anterior and posterior fascia of the rectus abdominis muscle.

Outcome measures

Baseline data were recorded prior to receiving the allocated treatment. Pain intensity was assessed by measuring pain using an 11-point numerical rating scale (NRS) scale, as per IMMPACT recommendation[25]. The primary outcome was the proportion of patients demonstrating a minimal 50% pain reduction on the NRS score at the 8 week time point following PRF or neurectomy. As neurectomy is still considered the gold standard in treatment of ACNES, patients in the PRF group were offered an optional one-way crossover to the neurectomy group whenever treatment result was not successful at this 8 week time point. Subsequently, for further analysis they were considered as a failure.

Secondary outcomes include the effect of PRF or neurectomy on quality of life measured by the Short Form-12 (SF-12)[26]; patient disability measured by the Pain Disability Index (PDI) and Brief Pain Inventory (BPI)[27,28] and treatment satisfaction measured by Patient Global Impression of Change (PGIC)[25]. Analgesic medication usage was scored following World Health Organization (WHO) pain steps[29]. The Douleur Neuropathiqué (DN4) was used in order to discriminate between neuropathic and non-neuropathic pain[30]. A 7-point version of the DN4 was used, with a cut-off point suggestive of neuropathic pain of >3 as proposed by Bouhassira et al[31]. The number of patients who did not need neurectomy was also measured to show the efficacy of PRF.

All participants completed a series of baseline questionnaires including the NRS pain score, BPI, PDI, SF-12 and the DN-4. Identical questionnaires supplemented by the PGIC scale were mailed to the subjects for completion after 8 weeks and again after 6 months.

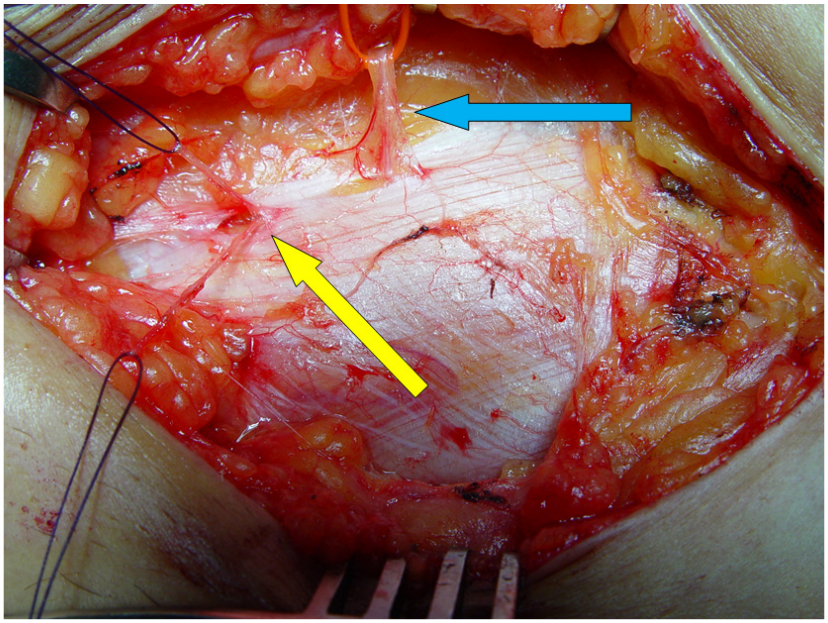

Figure 5.2:

Intraoperative view of a neurovascular bundle (loop, blue arrow) and nearby branches (loop, yellow arrow) perforating the fascial foramina of the anterior sheath of the abdominal rectus muscle during an anterior neurectomy for ACNES.

Statistics

The sample size was determined for the primary outcome, the proportion of successful response (minimal 50% improvement in pain perception). A previous sham controlled RCT on neurectomy in ACNES patients showed a 70% success in the neurectomy group[9]. Based on our retrospective case series and the available literature on PRF treatment, a 30% success rate was expected in the PRF group, almost one-third of patients could be spared a neurectomy[21]. The targeted effect size is a difference in proportion responding to treatment (neurectomy vs. PRF) of 40%; i.e., 70% responding in neurectomy group vs. 30% in the PRF group.However, less than 30% success rate was deemed insufficient. To be able to have 80% power to detect a difference between the success rate of neurectomy and PRF of 40% or more and a 5% type I error rate, 29 patients per group were required. Expecting a 10 percent loss to follow-up, 33 patients were included in each arm. Baseline patient characteristics were reported as mean and standard deviation (SD) and count and percentage, for continuous and categorical variables, respectively. In case of severe skewness of a continuous variable, median and interquartile range (IQR) were reported.

Differences in success rate between neurectomy and PRF were tested using Pearson's χ^2 test for categorical variables. The independent samples t-test was used to conduct between-group comparisons of outcomes. Secondary outcome measures were tested using the independent samples t-test or Mann–Whitney U test, depending on the distribution of the outcome. A p-value ≤ 0.05 was considered statistically significant.

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21 for Windows (IBM Corp. 2012, Armonk, NY).

RESULTS

Patients were recruited from October 1, 2015 to June 9, 2017. A total of 532 patients were assessed for eligibility. A total of 466 patients were excluded for reasons as depicted (Figure 5.3). As 35 patients did not consent to participation, 66 patients were randomized after informed consent (neurectomy: n = 33; PRF: n = 33). Four patients did not receive the allocated treatment (spontaneous remission, n = 3; withdrew consent, n = 1).

One patient terminated study participation after withdrawing consent before reaching the primary endpoint. One protocol violation was excluded since the affected nerve was iliohypogastric instead of an anterior cutaneous branch. Sixty patients (neurectomy: n = 28; PRF: n = 32) ended the study. Baseline characteristics and ACNES details were balanced between the 2 groups (Table 5.1).

Primary outcome

Before receiving intervention, pain levels were similar in the two groups (neurectomy 5.9 ± 1.4 vs PRF 5.7 ± 1.4). Regarding the primary outcome measure, the number of patients demonstrating a successful response after 8 weeks was higher in the group undergoing a neurectomy than PRF. However, no statistically significant difference was detected between groups (neurectomy, 61% (17/28) vs PRF, 38% (12/32); $P = 0.073$). Neurectomy participants experienced a greater percent change in NRS pain scores from baseline (-47.7, 95% confidence interval [CI] -64.8 to -30.6), than participants in the PRF group (-24.7, 95% CI -41.6 to -7.9; $P = 0.056$).

Secondary outcomes

Mean changes for secondary outcomes following either therapy are presented in Table 5.2. No between-group differences were found for quality of life, BPI severity scores or DN-4 scores at 8 weeks follow-up. Medication usage post-intervention was also not significantly different. However, patient satisfaction and BPI interference scores were higher in the neurectomy group after 8 weeks ($P = 0.019$ and $P = 0.044$, respectively). Quality of life scores measured on the SF-12 scale improved after either therapy, except the Mental Health Composite Score (MCS) at 8 weeks after PRF treatment. However, none of these results were significant.

Twelve PRF patients (38%) reported a successful treatment outcome after 8 weeks follow-up, although one chose to cross over to a neurectomy. On the other hand, two PRF patients declined a crossover at the 8 weeks follow-up moment due to a satisfactory pain relief, although they did not achieve the predefined successful outcome of >50% pain reduction. Therefore 13 out of 32 PRF patients did not receive a surgical intervention later on. Pre- and post-intervention pain scores of crossover patients were separately analyzed. Another 11 out of 19 PRF patients (58%) reached a successful outcome 8 weeks after surgery with a mean change in NRS scores after neurectomy in the crossover group of -2.5 ± 2.9.

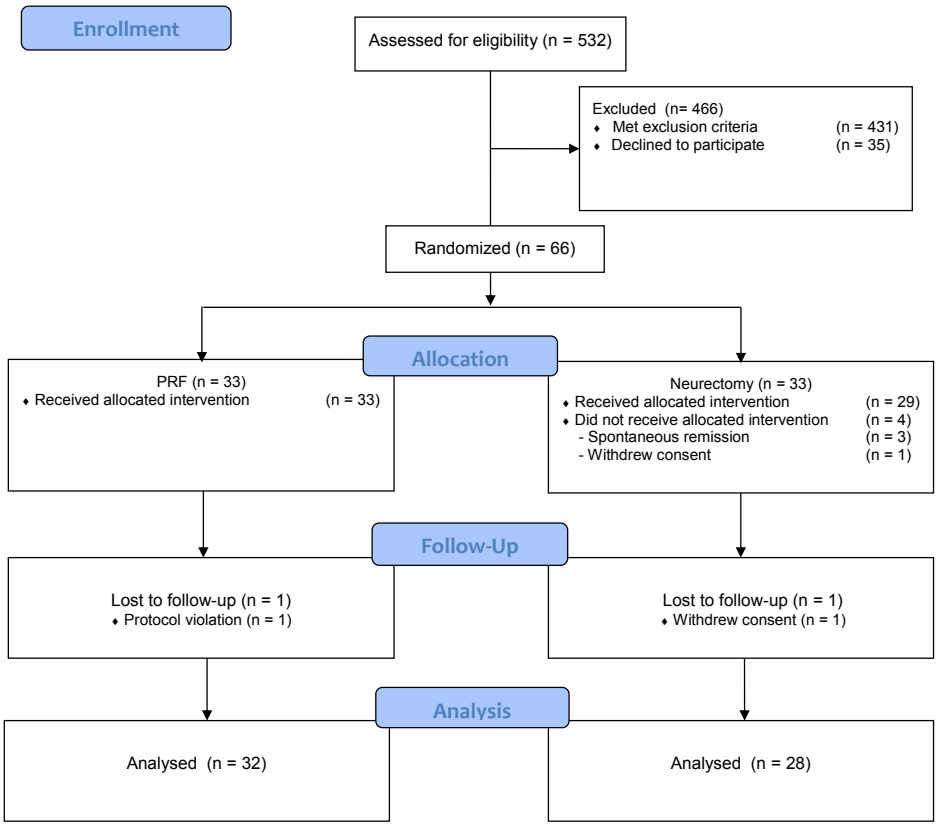

Figure 5.3:

CONSORT study diagram.

PRF: pulsed radiofrequency

Table 5.1:
Characteristics of ACNES patients randomized to a neurectomy or PRF

	PRF (n = 33)	Neurectomy (n = 33)
Age	40 [18-64]	43 [21-69]
Sex ratio, M:F	8:25	8:25
Height, cm	172 (10)	175 (11)
Weight, kg	80 (20)	82 (20)
BMI, kg/m²	27 (7)	27 (6)
Etiology, n		
Spontaneous	19	23
Sport	4	1
Pregnancy	1	0
Unusual activity	1	1
Recent abdominal surgery	8	8
Duration of pain before treatment, months	14 [3-180]	14 [3-120]
NRS	5.6 (1.4)	5.9 (1.3)
Physical component scale (SF-12)	32.9 (8.7)	33.5 (9.6)
Mental component scale (SF-12)	47.6 (8.6)	44.7 (11.1)
BPI_{SEV}	6.0 (1.3)	6.0 (1.4)
BPI_{INT}	4.1 (2.0)	4.9 (1.9)
PDI	35 (17)	37 (14)
DN4	3.0 [1.0-6.0]	3.0 [1.0-7.0]
Analgesic medication usage, n		
No medication usage	9	12
WHO step I	17	14
WHO step II	5	6
WHO step III	2	1
Abdominal pain location, n		
Right upper quadrant	10	8
Right lower quadrant	13	9
Left upper quadrant	4	2
Left lower quadrant	6	14

Descriptive statistics by treatment group. Means are presented with (SD) and medians with range. BMI: body mass index; NRS: numerical rating scale; BPI: brief pain inventory; PDI: pain disability index; DN4: douleur neuropathique 4; WHO: world health organization.

Table 5.2:
Secondary outcomes in ACNES patients 8 weeks after a neurectomy or PRF.

	Neurectomy group (n = 28)		Pulsed Radiofrequency group (n = 32)		Treatment comparison	
	Overall mean (SD)	**Mean change from baseline**	**Overall mean (SD)**	**Mean change from baseline**	**Mean difference (95% CI)***	***P***
BPI_{SEV}						
Baseline	6.0 (1.5)	N/A	6.1 (1.3)	N/A	N/A	N/A
8 wk	3.6 (2.8)	-2.4 (2.9)	4.4 (2.8)	-1.7 (2.5)	0.6 [-0.8 to 2.0]	0.365
BPI_{INT}						
Baseline	5.0 (1.7)	N/A	4.1 (2.0)	N/A	N/A	N/A
8 wk	3.1 (2.6)	-1.9 (2.7)	3.4 (2.8)	-0.6 (2.0)	1.2 [0.0 to 2.5]	**0.044**
PDI						
Baseline	37.5 (13.3)	N/A	35.1 (16.6)	N/A	N/A	N/A
8 wk	22.9 (16.9)	-14.6 (19.9)	28.0 (19.6)	-7.1 (16.4)	8.4 [-0.6 to 17.4]	0.065
DN4						
Baseline	3.1 (1.884)	N/A	2.8 (1.5)	N/A	N/A	N/A
8 wk	2.3 (2.106)	-0.8 (2.2)	2.4 (1.7)	-0.3 (1.8)	0.4 [-0.6 to 1.5]	0.392
SF-12 – PCS						
Baseline	32.3 (9.3)	N/A	32.4 (8.4)	N/A	N/A	N/A
8 wk	38.8 (9.2)	6.6 (11.8)	36.2 (11.3)	3.9 (8.8)	-2.7 [-8.1 to 2.6]	0.311
SF-12 – MCS						
Baseline	44.4 (11.3)	N/A	47.6 (8.8)	N/A	N/A	N/A
8 wk	47.9 (9.8)	3.8 (10.3)	46.6 (11.4)	-1.0 (10.3)	-4.8 [-10.2 to 0.6]	0.080
PGIC	5.5 (1.5)	N/A	4.5 (1.7)	N/A	N/A	**0.019**

** Mean changes compared with baseline outcome values. Negative coefficients favor the pulsed radiofrequency group, whereas positive values favor neurectomy.*

Long-term follow-up of PRF

Study outcomes of participants at long-term follow-up are shown in Figure 5.4. The proportion of patients reporting a lasting successful response at the 6 month follow-up point was significantly higher in the group undergoing a neurectomy compared to PRF (neurectomy, 50% (14/28) vs PRF, 13% (4/32); $P = 0.013$). Seven patients lost the initial positive outcome of PRF, of which 5 choose to a repeat PRF treatment procedure leading to success in four. Two patients did not show the predefined successful outcome but preferred no additional intervention.

Adverse events

Four patients experienced complications during the study period. In the surgery group complications included infection (n = 1, antibiotics and drainage) and temporary increased level of local pain (n = 2). In the PRF group, one patient experienced a temporary increase of pain level following intervention which required additional pain medication.

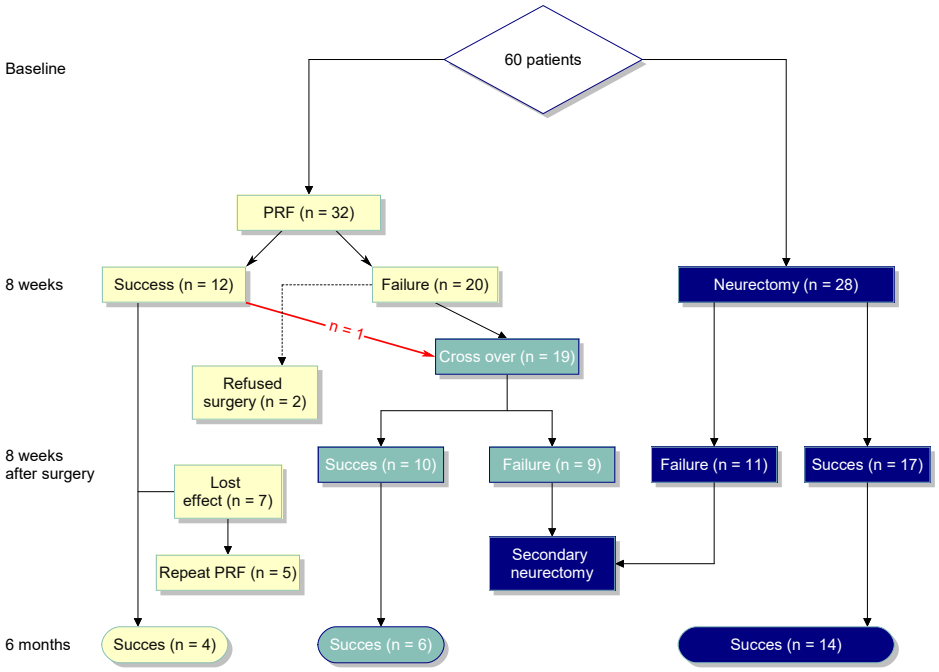

Figure 5.4:

Treatment flowchart.

Successful outcome is defined as >50 % reduction of pain; PRF: pulsed radiofrequency.

DISCUSSION

In recent years, several studies in ACNES have established that surgery such as a neurectomy at the level of the anterior rectus sheath is effective at long term follow-up in the majority of patients who do not have a sufficient pain relief after conservative treatment including an injection regimen.[5,32,33] While very few complications were reported after neurectomy, less invasive treatment options may also be beneficial as suggested by two case reports.[19,20] This clinical trial is the first to demonstrate the efficacy and safety of PRF treatment in ACNES patients in a randomized controlled setting. In our study, 4 of 10 patients reported success at the short-term. Moreover, 13 patients (40%) withdrew from a scheduled neurectomy. Although this type of surgery is associated with very few complications, PRF could lead to fewer surgical interventions in a random ACNES population and thereby costs are likely reduced as general anaesthesia and hospitalization are avoided.

There are several clinical studies that earlier demonstrated anti-nociceptive effects of PRF treatment in a variety of neuropathic pain syndromes.[17,18,34] Since an initial report in 1998, PRF is increasingly recognized as a popular tool in various chronic pain conditions.[13,35] However, in modern-day era of evidence-based medicine, any novel treatment should proof itself in clinical trials prior to widespread introduction. PRF is an example of such a new treatment that is increasingly used for a variety of conditions but sometimes with rather limited scientific evidence.[36,37] The present study is the first to show the efficacy of the peripheral use of PRF in a randomized and controlled setting in a neuropathic pain syndrome such as ACNES.

One aim of our study was to determine whether PRF treatment would lead to fewer surgical interventions in a random ACNES population. Eventually 12 out of 32 PRF patients (38%) reported by definition a successful outcome at 8 weeks follow-up. Subsequently, 13 patients (40%) had declined surgery at 6 months. One might argue that minimally invasive techniques such as PRF are mainly considered for short term relief.[38] However, our results also show that 4 out of the initially successful treated 12 patients (33%) still had a successful outcome after 6 months. This finding is in line with other reports and strengthens the long term potential of this treatment modality.[35,39] Therefore, due to its minimal invasive nature and potential beneficial outcomes, one may argue that PRF should be offered to patients with just short-lived effect of infiltrations with lidocaine and other conservative measures, prior to proceeding to a surgical intervention.

One may argue that the abdominal wall injection might not be related to nerve entrapment as a myofascial trigger point could be present. Abdominal myofascial pain syndrome (AMPS) might mimic some characteristics of ACNES, making it difficult to distinguish between the two entities. One study by Niraj et al. stated that myofascial trigger points do *not* occur at the lateral borders of the rectus muscle, and do not express signs of nerve irritation (e.g. abnormal skin sensibilities).[43] This is in sharp contrast with ACNES, where patients report their pain alongside the lateral borders of the rectus muscle and patients complain of cutaneous allodynia or hypoesthesia.[44] Furthermore, there exist some other differences between the abdominal myofascial pain syndrome (AMPS) and ACNES.[45-48] Contrary to ACNES, skin pinching in AMPS is usually normal, as is the local skin sensibility covering the painful area. Moreover, gender distribution is almost equal (females:males = 54:46).[47]

A limitation of the present study is its non-blinded design as blinding was practically impossible. However, it is unlikely that an unblinded approach resulted in biased estimates of between-group differences as two active treatments were compared. Furthermore, all patients presented to our clinics after a substantial diagnostic delay (median 14 months) so a beneficial effect of PRF is not likely solely due to a placebo effect since all prior therapies failed to achieve success. Another potential limitation is the fact that the abdominal wall injections were done by a free-hand technique possibly resulting in not reaching the targeted location or therefore being less effective. This procedure could also be guided by ultrasound feasibly resulting in a more accurate approach. Thirdly, the 8 weeks evaluation time point rather than 3 months, largely

acknowledged as a cut-off point for chronic pain.[49] However, it was considered unethical to refrain patients from a neurectomy procedure beyond 8 weeks as this is the average waiting time for an operation. Since this is a proof-of-concept trial, we allowed cross-over to the neurectomy group in order to keep the pain burden to a minimum. As a result, knowledge of the enrolled patients to be able to have the planned procedure (i.e. a neurectomy) if they receive insufficient pain relief from PRF, could also have affected pain score reporting. Finally, being a tertiary referral center for abdominal wall related pain, results may not immediately be extrapolated to an average clinical practice due to potential referral and selection bias. On the other hand, study participants had failed our conventional injection regimen as proposed to newly diagnosed ACNES patients.[5] As a consequence, treatment efficacy may have been underestimated since all patients were non-responders to previous conservative regimens.

The present randomized trial demonstrates the efficacy of both surgery and PRF in ACNES patients who are refractory to conservative pain treatment strategies. Subsequently, pain relief following PRF as a minimally invasive and safe treatment option also confers reasonable outcomes in a portion of ACNES patients. It may be considered to incorporate PRF into the ACNES treatment algorithm prior to deciding on a surgical exploration.

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CHAPTER 6

Chronic localized back pain due to posterior cutaneous nerve entrapment syndrome (POCNES): A new diagnosis

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SUMMARY

Most patients with chronic back pain suffer from degenerative thoracolumbovertebral disease. However, the following case illustrates that a localized peripheral nerve entrapment must be considered in the differential diagnosis of chronic back pain.

We report the case of a 26 year-old woman with continuous excruciating pain in the lower back area. Previous treatment for nephroptosis was to no avail. On physical examination the pain was present in a 2x2 cm area overlying the 12th rib some 4 cm lateral to the spinal process. Somatosensory testing using swab and alcohol gauze demonstrated the presence of skin hypo- and dysesthesia over the painful area. Local pressure on this painful spot elicited an extreme pain response that did not irradiate towards the periphery. These findings were highly suggestive of a posterior version of the anterior cutaneous nerve entrapment syndrome (ACNES), a condition leading to a severe localized neuropathic pain in anterior portions of the abdominal wall.

She demonstrated a beneficial albeit temporary response after lidocaine infiltration as dictated by an established diagnostic and treatment protocol for ACNES. She subsequently underwent a local neurectomy of the involved superficial branch of the intercostal nerve. This limited operation had a favourable outcome resulting in a painfree return to normal activities up to this very day (follow-up of 24 months).

We propose to name this novel syndrome 'posterior cutaneous nerve entrapment syndrome' (POCNES). Each patient with chronic localized back pain should undergo simple somatosensory testing using to detect the presence of overlying skin hypo- and dysesthesia possibly reflecting an entrapped posterior cutaneous nerve.

INTRODUCTION

Most patients with chronic back pain suffer from degenerative thoracolumbovertebral disease. However, the following case illustrates that a localized peripheral nerve entrapment must be considered in the differential diagnosis of chronic back pain.

Case

A 26-year-old woman presented with a continuous excruciating right sided back pain. She was not able to stand for even a short period of time and was heavily impaired in her work as a fashion designer. Lying down attenuated the symptoms. Her medical history revealed a right sided nephroptosis for this back pain that was treated twice by a laparoscopic nephropexia but to no avail. After consulting with several pain specialists, she was referred to Maasziekenhuis Pantein as part of an abdominal wall pain studygroup, since a non-urological, neuropathic origin of the pain was suspected.

On physical examination, the pain was present in a 2x2 cm area overlying the 12th rib some 4 cm lateral to the spinal process (Figure 6.1).

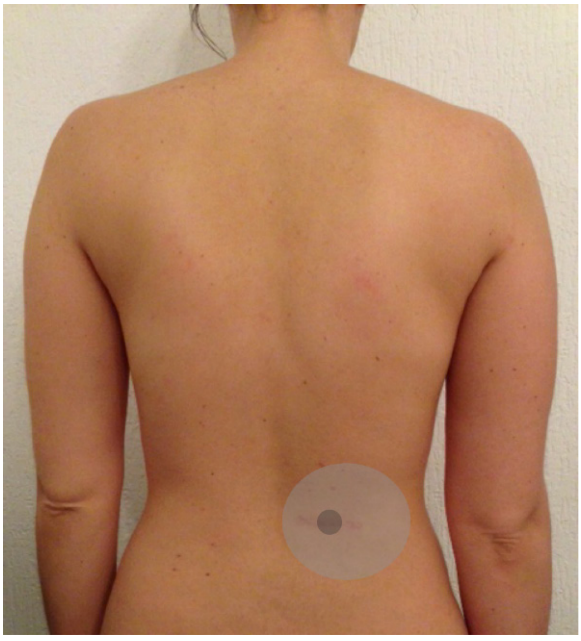

Figure 6.1:

Back of the patient 6 months after surgery, showing the neurectomy scar over the previous area of allodynia (shaded in a lighter gray). Centrally, the point of maximum pain is marked (shaded in dark grey).

This area was not in proximity to any surgical scar or previous laparoscopic trocar sites. Somatosensory testing using swab and alcohol gauze demonstrated the presence of skin hypo- and dysesthesia over the painful area. Local pressure on this 2x2 cm spot elicited an extreme pain response that did not irradiate towards the periphery. As signs and symptoms strongly suggested a cutaneous nerve entrapment syndrome such as in ACNES[1]. The trigger point was infiltrated subfascially by a freehand technique using 2 ml of 1% Lidocaine. This resulted in an immediate albeit temporary relief. Therefore, a superficial entrapment was deemed highly likely. As two additional infiltrations using a mix of Lidocaine and Methylprednisolone were not successful on the long term, specifics of a surgical procedure were discussed.

Following written consent, the point of maximal pain was surgically explored via a small transverse incision. The posterior end branch of the 12th intercostal nerve penetrating the fascia of paravertebral muscles was identified followed by resection (Figure 6.2 and 6.3). At the 6 weeks follow up she was pain free. After twenty-four months, only minimal discomfort was reported without interference of daily activities.

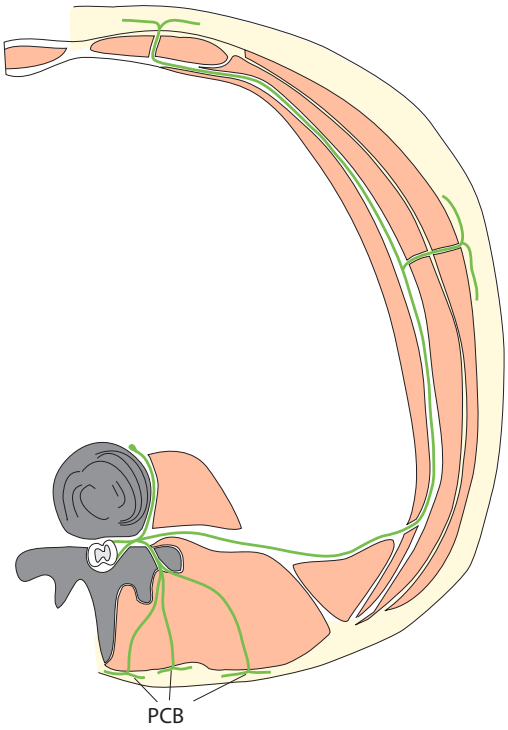

Figure 6.2:

Schematic representation of the anatomy of the intercostal nerve.

PCB = posterior cutaneous branches.

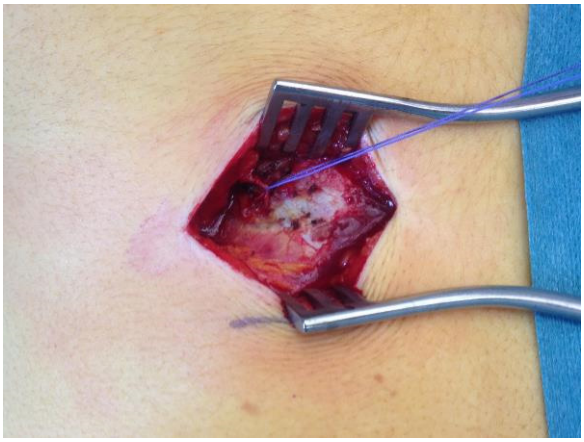

Figure 6.3:

Perioperative view of the perforating posterior cutaneous branch of intercostal nerve (looped by ligature).

To our knowledge, this report is the first in literature to identify a patient with a –to this date unknown- diagnosis of posterior cutaneous nerve entrapment syndrome (POCNES). The diagnosis is well explained on the basis of its anatomical features whereas the diagnostic tests are straightforward. Treatment modalities including injections and surgery confirm the diagnosis with a successful short term en long term result as also observed in a related diagnosis of ACNES (anterior cutaneous nerve entrapment syndrome)[2].

High level evidence literature for ACNES is sparse[3]. Anterior branches of an intercostal nerve are somehow trapped in abdominal muscles causing severe pain. A recent randomized trial including a sham operation unambiguously confirmed the validity of a theoretical-anatomical model of a painfully entrapped intercostal nerve[4]. Once ACNES is properly diagnosed, treatment is simple and successful[2]. Over 80% of patients experience an immediate pain relief following trigger point injections using a local anaesthetic agent (with or without corticosteroids), whereas 32% also report long term pain relief. Subsequent surgical treatment in refractory patients results in a 70% long term positive result in neurectomized patients[2,4].

With these data in mind and reflecting on anatomy it must be appreciated that an intercostal nerve also has lateral and posterior branches. In literature just one case reported of a chronic flank pain patient undergoing a neurectomy of entrapped *lateral* branches of the intercostal nerve[5]. In a systematic literature search however, neither similar case reports or series suggesting a *posterior* cutaneous nerve entrapment syndrome nor a theoretical-anatomical description of this phenomenon were found. Considering the sparse literature on ACNES and a long doctor's delay, POCNES is likely overlooked as well. Therefore, an estimate of the true incidence of this diagnosis is not available.

In conclusion, the term posterior cutaneous nerve entrapment syndrome (POCNES) is proposed for this novel syndrome. General practitioners, neurologists, (orthopaedic) surgeons as well as pain specialists should consider POCNES in the differential diagnosis in each patient with chronic localized back pain in the presence of overlying skin hypo- or dysesthesia on simple somatosensory testing using a swab and an alcohol gauze. This set of findings may reflect an entrapped posterior cutaneous nerve.

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CHAPTER 7

Chronic localized back pain due to entrapment of cutaneous branches of posterior rami of the thoracic nerves (POCNES): A case series on diagnosis and management

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ABSTRACT

Objective: Chronic back pain (CBP) may be caused by a variety of conditions including dysfunctional muscles, ligaments or intervertebral discs, improper movement of vertebral column joints or nerve root compression. Recently, CBP was treated successfully in a patient having an entrapment of cutaneous branches of the posterior rami of the thoracic nerves termed posterior cutaneous nerve entrapment syndrome (POCNES). Our aim is to describe clinical presentation, differential diagnosis and management of patients with such a neuropathic pain syndrome.

Methods: This study analyzed prospectively obtained data of consecutive patients suspected of having POCNES, presenting to two Dutch hospitals between January 2013 and September 2016. Patients received a diagnostic 2-5 mL 1% lidocaine injection just below the thoracolumbar fascia. Pain was scored using a numerical rating scale (0, no pain to 10, worst possible). A >50% pain reduction was defined as success. A neurectomy was proposed if pain reduction was temporary or insufficient after 1-3 injections. Long term treatment effect was determined using a verbal rating scale (VRS; 1, very satisfied, no pain to 5, pain worse).

Results: Fourteen patients (12 women, median age 26, range 18-73) were diagnosed with POCNES. Eighty-one percent (n=11) reported a >50% pain drop after injection (median 8.0 (interquartile range 7.0-8.0) to median 3.0 (interquartile range 1.5-3.5), $p<0.001$). In one patient, rpeated injections were long term successful (VRS 2). Two patients declined surgery, whereas the remaining eleven underwent a neurectomy that was successful in 7 (64%). A 57% long-term efficacy (median 29 months follow-up, range 5-48, VRS 1-2) was attained in the whole study population.

Conclusion: Posterior cutaneous nerve entrapment syndrome (POCNES) should be considered in the differential diagnosis of chronic localized back pain. A treatment regimen including injections and neurectomy of the specific cutaneous branch results in long term pain relief in more than half of these patients.

INTRODUCTION

Approximately 80% of the global population will experience acute lower back pain at some point in life, and 5-10% will go on to develop chronic back pain (CBP) resulting in a major health burden[1-3]. CBP may be due to mechanical dysfunctioning, a neuropathic disorder, or secondary to other conditions while the differential diagnosis is extensive[4-8]. CBP often requires a multimodal treatment stratagem, but pain relief on the long term is often suboptimal[5,9,10].

A recent case report attracted attention to a novel syndrome causing CBP termed posterior cutaneous nerve entrapment syndrome (POCNES)[11]. This condition is supposedly due to irritation of cutaneous branches of the posterior rami of the thoracic spinal nerves by an unknown cause. The patient reported a neuropathic pain that was accompanied by sensations such as localized hyperalgesia and allodynia[12,13]. The differentiation between neuropathic and non-neuropathic pain is always challenging, but neuropathic signs and symptoms may be suspected during extensive history taking using specific questionnaires suggesting neuropathic pain such as DN-4, or following simple tests during physical examination[14-16]. Ultimately, a simple neurectomy abolished the severe pain that had bothered her for years. While the number of studies on a localized neuropathic anterior *abdominal* pain (anterior cutaneous nerve entrapment [ACNES]) is steadily increasing, chronic localized (lower) *back* pain that is caused by an entrapped cutaneous branch of the posterior ramus of the thoracic spinal nerve is thought to be a new phenomenon and not yet known to the medical community.

The department of General Surgery/SolviMáx has gained ample expertise in the management of neuropathic pain syndromes of the trunk including ACNES[17,18]. This abdominal wall pain syndrome is possibly caused by the entrapment of *anterior cutaneous* branches of thoraco-abdominal intercostal nerves at a specific point of the ventral portions of the abdomen. These nerves are usually anchored at three sites: (1) at the back where the posterior branches of the thoracic nerve originate, (2) at the flank where the lateral branch originates and (3) at the anterior abdominal wall where the nerve enters the rectus abdominis muscle (Figure 7.1)[19]. A previously mechanical theory suggested that a too tight anchor may cause ischemia and severe pain at any of these three locations[20].

Aim of our study is to describe a series of CBP patients who were diagnosed and treated for possible entrapment of cutaneous branches of the posterior rami of the thoracic spinal nerves (posterior cutaneous nerve entrapment syndrome, POCNES). Awareness regarding this unknown condition may thus be increased.

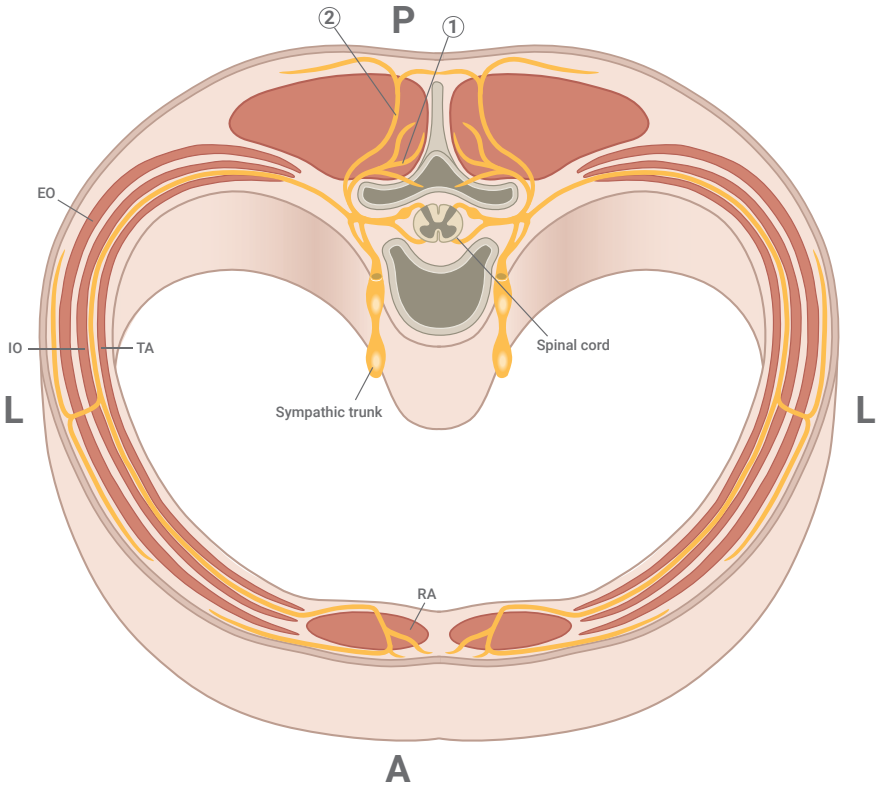

Figure 7.1:

Anatomy of a thoracic spinal nerve with the intercostal cutaneous nerve originating from ventral ramus.

The posterior ramus divides in a medial (articular) branch (1) and the cutaneous branch of the posterior ramus of the thoracic spinal nerve (2). The group of muscles pictured lateral of the spinous process are the erector spinae muscle. Abbreviations: A, anterior; EO, external oblique muscle; IO, internal oblique muscle; L, lateral; P, posterior; RA, rectus abdominis muscle; TA, transverse abdominal muscle.

METHODS

Setting

This prospective case series was conducted at Departments of General Surgery of two Dutch hospitals, Pantein Hospital (PH), Boxmeer and Máxima Medical Center (MMC), Eindhoven/Veldhoven between January 2013 and December 2016. Surgeons of both centers have a special interest in the management of chronic pain syndromes of abdominal wall and groin[18,21,22]. Both local ethics committees of the two participating hospitals approved the study protocol and decided that the Medical Research Involving Human Subjects Act (in Dutch: WMO) did not apply (N17.009). The present analysis was considered auditing of results and evaluation of patient-reported outcomes. All patient data were anonymized. The present study follows guidelines of the declaration of Helsinki (version October 19th, 2013).

Patient assessment

After a letter of referral including history, earlier physical examinations, laboratory testing and imaging that were performed elsewhere is screened by one of three senior surgeons (OB, MS and RR) skilled in the management of abdominal wall and groin pain, a patient is invited to undergo an outpatient assessment in one of the two hospitals. An outpatient evaluation is started with an extensive history taking, focusing on aspects of pain including provocative movements and earlier therapies, as well specifically on neuropathic pain (Douleur Neuropathique, DN4)[23]. Physical examination includes a series of standard tests[24,25]. The patient is asked to indicate the location of maximum pain. Skin tactile sensibility and sensitivity to cold was tested using a cotton swab and an alcohol soaked gauze to detect somatosensory disturbances such as hypoesthesia, hyperesthesia and/or altered cool perception in proximity of the painful area. Furthermore, 'pinching' the skin overlying the painful area using thumb and index finger is often painful in comparison to the contralateral side. This phenomenon is called a positive Pinch test and is suggestive of neuropathic pain[24,26]. Local pressure on the specific tender point may also result in a disproportionally painful response.

While most of these patients are referred for evaluation of a chronic abdominal or groin pain, small subsets were found to have pain located at the flank, or at the back[11,25]. Therefore, inclusion criteria for the diagnosis POCNES are based on a large (but subjective) experience in patients with ACNES and lateral cutaneous nerve entrapment syndrome (LACNES)[17,25]. Patients aged >18 were eligible for inclusion in the present case series if at least 4 out of 5 the criteria show in Table 7.1 were met.

Absence of objective abnormalities in either laboratory testing or imaging techniques as earlier determined in the referring hospital confirmed a cause for chronic back pain other than a mechanical cause (e.g. degenerative thoracolumbar disease) or a referred pain from visceral disease (e.g. kidney stones). Results of history and physical examination that were tabulated in a standard outpatient evaluation form and were stored in the hospital's electronic patient file.

Table 7.1:
Inclusion and exclusion criteria for posterior cutaneous nerve entrapment syndrome (POCNES).

Inclusion criteria
1) A >3 month history of locoregional back pain
2) A localized circumscript area of tenderness lateral to the spinous process, covering a small and predictable point of maximal pain
3) A larger area of skin somatosensory abnormalities (such as hypoesthesia, hyperesthesia and/or altered cool perception) overlying this maximal pain point
4) Local pressure on the tender point resulting in a predictable severe pain response
5) Normal laboratory testing and imaging
Exclusion criteria
1) Surgical scar-related pain syndromes
2) Previous spinal surgical procedures at or between vertebral levels T7-L1
3) Impaired communication

Current management

If patients met at least 4 of 5 diagnostic criteria as shown in Table 7.1, a presumptive diagnosis of POCNES was communicated and specifics of a diagnostic injection of an anesthetic agent were discussed. After informed consent was obtained, patients were placed prone on a stretcher. After skin disinfection, an injection of 2-5mL 1% lidocaine just underneath the thoracolumbar fascia was administered using a 21 G 40 mm needle. Volume was based on patient's weight and/or subcutaneous thickness around the tender point. Needle tip placement is just below the thoracolumbar fascia of the erector spinae muscle, ideally into or in close proximity to the tender point using a free hand technique, as previously published for ACNES or LACNES[24,25]. Pain was then scored using a numerical rating scale [NRS, 0 (no pain) to 10 (worst possible pain)] immediately before and after a 10-15 minutes observation period. If levels of pain were considerably lower (e.g. >50% pain reduction) or absent by then, characteristics of the diagnosis were again communicated, and the patient was evaluated some 2-3 weeks later. If the pain had recurred at this first outpatient control, a combination of 2-5 mL of 1% lidocaine and 40 mg of methylprednisolone was administered. When the effect of repetitive injections on experienced pain levels by patients was inadequate (e.g. <50% pain reduction) or if patients declined ongoing injection therapy, patients were informed on alternative treatments including medication, physical therapy, manual therapy, Transcutaneous Electrical Nerve Stimulation (TENS) or (pulsed)radiofrequency therapy (pRF). If alternative therapy modalities were to no avail or denied, a surgical exploration was proposed. Specifics of the surgical procedure were communicated. If surgery was preferred, patients consented verbally and in writing to the operative procedure.

Surgical procedure

Localized surgical techniques as treatment for low back pain have been described in the early 1970s by Rees et al[27]. He described a percutaneous rhizolysis technique for supposed facet pain. Our surgical procedure is different since it requires a neurectomy of the lateral branch of the posterior rami instead of the medial branch which innervates the zygapophysial joints[28,29]. Patients were operated in a day care setting. While lying in prone position, the point of maximal pain was again identified and marked. Once general anesthesia was administered, the thoracolumbar fascia was exposed via a transverse ±5 cm long skin incision. The neurovascular bundle penetrating the subcutaneous fat was identified. The fascial window was widened and the nerve as well as all of its branches within a 5-cm radius were ligated and removed (Figure 7.2). Accompanying vascular structures were ligated or coagulated. The fascia and the remainder of the wound were closed in layers using absorbable suturing material. The patients received a control visit at the outpatient department approximately 6 weeks postoperatively.

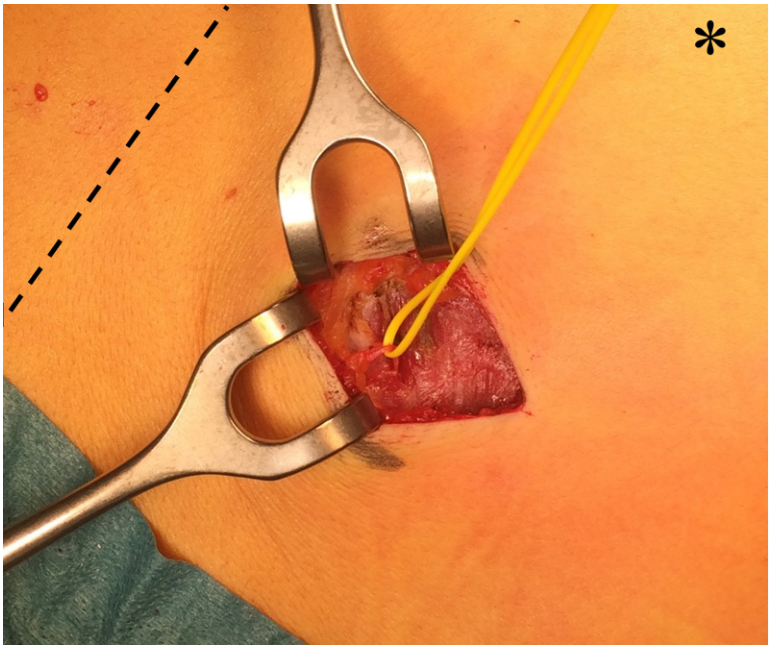

Figure 7.2:

Perioperative view of a cutaneous branch of the posterior ramus of a thoracic nerve (looped by ligature) perforating the thoracolumbar fascia.

The transverse incision was made exactly over the pain point (marked with black ink) which was in the paravertebral region some 4-5 cm lateral to the midline (the dotted line). The asterisk indicates cranial in the prone patient.

Data accrual

A search of the hospital's electronic patient system was performed by the first author using a surgical diagnosis code that was exclusively assigned to abdominal wall and groin related pain syndromes. Data regarding age, gender, body mass index, diagnostic delay, etiology, NRS scores, DN4 scores, time of follow-up, date of being pain free or possible recurrences were entered in a separate database. A 7-point version of the Douleur Neuropathiqué (DN4), with a ≥3 cut-off point suggestive of neuropathic pain was used in order to discriminate between neuropathic and non-neuropathic pain[23,30]. Numerical Rating Scale (NRS) was used to score pain on a 0 (no pain) to 10 (worst possible pain) scale at baseline and during follow-up at the outpatient clinic. Treatment success was defined as >50% pain reduction on the NRS scale. A final follow-up control to assess long-term clinical outcomes was done by a standardized telephone interview that included questions on current satisfaction and long term complications. Level of satisfaction was determined as previously published (Table 7.2)[24]. Clinical success was defined as a VRS of 1 or 2 ([very] satisfied), while a VRS of 3 was defined as an attenuated pain level. The therapy had failed if the patient reported a VRS of 4 or 5.

Table 7.2:
Level of satisfaction after treatment for ACNES using Verbal Rating Scale*.

1	I am very satisfied; I have no pain anymore.
2	I am satisfied; I occasionally experience some pain.
3	I have improved, but experience some pain on a regular basis.
4	The treatment did not change my pain level.
5	My pain has worsened after the treatment.

Reproduced from Boelens OB, Scheltinga MR, Houterman S, Roumen RM. Management of anterior cutaneous nerve entrapment syndrome in a cohort of 139 patients. Ann Surg. 2011;254(6):1054–1058.24[17]. Abbreviation: ACNES, anterior cutaneous nerve entrapment syndrome.

Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21 for Windows. The sample size was determined pragmatically as a total of 14 patients that met our eligibility criteria were identified in our centers. Categorical variables were described as frequencies. Continuous data were tested for normality and are presented as means with standard deviation (±SD) or median values (range) as appropriate. Changes in pain scores after lidocaine infiltration were evaluated using paired T-testing. A p-value of <0.05 was considered significant.

RESULTS

Baseline patient characteristics

During a 4 year observation period, 14 patients (12 females; median age, 26 years; range 18-73 years) fulfilled inclusion criteria. Demographics are depicted in Table 7.3. All patients had undergone extensive earlier laboratory testing and imaging (ultrasound imaging, computer tomography, and/or magnetic resonance imaging scan) to exclude any visceral or mechanical underlying cause, mostly performed elsewhere. All showed no specific abnormal findings. All patients had a score of minimal 3 on the DN4 questionnaire (median 3, range 3-5) confirming a neuropathic pain syndrome. Interestingly, six of the patients had undergone an anterior neurectomy (success, n=3) for ipsilateral ACNES at an earlier stage.

Location of the point of maximum tenderness was distributed between the inferior angle of scapula and the lowest costal margin. The point of maximal pain corresponded in half of the cases (n=7) with the cutaneous branches of the posterior rami of the twelfth thoracic spinal nerve. A positive pinch test was found in 86% (12/14). Combinations of various somatosensory disturbances were observed in all. There was no preponderance for left vs right. Two patients had a bilateral pain syndrome.

Table 7.3:
Characteristics of patients with POCNES.

	n = 14
Age (range)	26 (18 - 73)
Gender, F:M ratio	12 : 2
Body mass index, kg/m² (SD)	23 (3)
Diagnostic delay, months (range) of duration of pain	22 (5 - 48)
Pain level at presentation (NRS, 0-10), (IQR)	8.0 (7.0 - 8.0)
DN4 (range, 0-7)	3.0 (3.0 - 5.0)
Previous neurectomy for ACNES	6

Data are presented as mean with standard deviation (± SD), or median values with ranges. NRS, Numerical Rating Scale. IQR, interquartile range. DN4, Douleur Neuropathiqué 4.

Injection therapy (n = 14)

Interventions are depicted in Table 7.4. All consented to a diagnostic maximal pain point infiltration using 2-5 ml of 1% lidocaine. Pre- and post- NRS scores (13 of 14 patients, 93%) dropped from 8.0 (median, interquartile range 7.0–8.0) to 3.0 (median, interquartile range 1.5-3.5), $p < 0.001$). Ten of 13 patients (81%) reported a >50% pain reduction. All 14 patients experienced partial or temporary relief, whereas 11 reported pain relief for days to several weeks (Table 4). Just one patient opted to continue with incidentally repeated injections and her pain level was acceptable in the long term (13 months follow-up; VRS = 2). Injection therapy was insufficient in the remaining 13 patients who all opted for subsequent alternative treatments.

Table 7.4:
Characteristics and treatment success of individual POCNES patients.

	Patient characteristics				Diagnostic Injection		Treatment & follow-up					
Pt	Age	Gender	Location	Pain area in corresponding dermatome	NRS pre	NRS post	Number of injections	Duration of relief post-injection	Neurectomy	Pain specialist	Final VRS[a]	Duration
1	19	M	Left	T8	7	2	3	Days	Y	N	2	20
2	21	F	Right	T12	7	0	1	Weeks	Y	N	2	20
3	50	M	Right	T12	8	4	2	Days	Y	N	4	31
4	18	F	Right	T12	8	1	1	Days	Y	N	4	33
5	24	F	Right	T10	7	3	2	Hours	Y	N	4	36
6	18	F	Bilateral	T7	9	0	2	Days	Y	N	1	27
7	26	F	Right	T12	7	3	3	Days	Y	N	1	48
8	48	F	Left	T8	8	3	2	Days	Y	N	1	16
9	46	F	Left	T12	6	3	2	Days	Y	N	2	5
10	20	F	Left	T8	8	4	2	Days	Y	N	2	47
11	28	F	Left	T11	7	3	1	Hours	N	Y	4	13
12	43	F	Bilateral	T12	-	-	2	Weeks	N	Y	4	37
13	26	F	Right	T12	8	5	2	Hours	Y	N	4	32
14	73	F	Left	T11	9	2	9	Weeks	N	N	2	13

NRS Numerical Rating Scale pre/post injection. – Missing data. [a] Long term success at FU is defined as attaining final VRS 1 or 2 (corresponding with >50% pain reduction, n=8) after receiving one or more interventions.

Surgery (n = 11)

Eleven patients chose to undergo a neurectomy (79%, Table 7.4). At the 6-week postoperative evaluation, 7 patients (64%) were (very) satisfied (VRS 1 or 2) whereas 3 (27%) reported attenuated pain levels (VRS 3). Surgery was unsuccessful in one patient (VRS 4). A VRS 5 was not scored. A 100% response rate of the 11 operated patients was attained in the long term (median 29 months, range 5 – 48), and seven (64%) were satisfied (VRS 1-2). Surgery was unsuccessful in the remaining four (36%, VRS 4). One initially successful patient (VRS 1) reported a recurrence of pain (VAS 4). No VRS 5 was scored.

Non-surgical treatment (n = 3)

Three patients declined surgery and underwent alternative therapies (repeated injection therapy, (p)RF therapy and TENS). One patient was satisfied in the long term (13 months, VRS 2, injection therapy). However, the two others reported an unsuccessful result (VRS 4) of these therapies (pRF and TENS) after, 13 and 37 months, respectively.

DISCUSSION

The present case series reports on patients having a chronic localized (lower) back pain syndrome that is caused by an entrapped cutaneous branch of the posterior ramus of the thoracic spinal nerve, most commonly in the T11-12 area. The term POCNES has recently been introduced for this new pain entity. These patients report pain characteristics mimicking ACNES or LACNES, but the point of maximum pain is located at the lower paravertebral region rather than in the ventral or lateral portions of the trunk or abdomen. Aim of the present study was to describe clinical presentation, differential diagnosis and management of a series of these patients. A simple step up treatment regimen including injections and neurectomy resulted in a long-term pain relief in more than half (57%) of these patients. It should be appreciated that the median time of duration of our patients having this undiagnosed (lower) back pain syndrome approximated two years before the diagnosis POCNES was considered. Based on a characteristic patient's history (localized pain) and physical examination (point of maximal pain in an area having somatosensory disturbances), this novel pain syndrome should be considered in the differential diagnosis of each patient with CBP in the presence of overlying somatosensory disturbances.

To our knowledge, this is the first case-series reporting on a pain syndrome possibly caused by entrapment of cutaneous branches of posterior rami of thoracic nerves. In recent years, an increasing number of studies were published on an anterior variant of entrapped intercostal nerves (ACNES)[17,18,21,24,31]. However, reflecting on anatomy it should be realized that the thoracic nerves also have posterior branches. Other groups reported on two patients having a pain entity due to possible entrapment of lateral branches of intercostal nerves[32,33]. A larger case series on this entity (LACNES)

was published recently[25]. The first case report on a posterior version of ACNES with involvement of posterior cutaneous branches of thoracic nerves resulting in severe lower back pain appeared in 2017[11]. It is our understanding that, although patients present with pain at different locations (e.g. anteriorly, laterally or posteriorly), the 3 pain syndromes (ACNES, LACNES and POCNES) have a high degree of overlap in signs and symptoms at physical examination and history and may be different expressions of a similar underlying thoracic spinal nerve pain syndrome.

Current detailed textbook descriptions of the anatomy of the thoracic dorsal rami vary and are limited[34-36]. Dorsal or posterior rami are thought to divide in medial and lateral branches, while the latter branches into a medial and lateral twig (Figure 7.1). Medial branches innervate the zygapophysial joints and the multifidus muscle, while lateral branches innervate the iliocostalis and longissimus muscle and overlying skin [28,29]. The main lateral branch runs caudally, laterally and dorsally underneath the longissimus muscles and descends approximately two vertebral segments caudally before it pierces the thoracolumbar fascia. It than divides in a medial (sometimes referred to as 'intermediate') and lateral cutaneous branch providing skin sensation[28,29,37]. This rather complex and possibly variable anatomical course of dorsal rami may explain why this cause for chronic localized back pain has been overlooked until now, as is often the case in other neuropathic abdominal wall pain syndromes[25,38,39]. The first POCNES case report raised awareness regarding this particular presentation of symptoms and resulted in the identification of more cases over the following years[11].

The description of a novel syndrome is greatly aided if a clear list of criteria regarding history and physical examination is identified. Pivotal is pain that is characterized by a constant and predictable site of local tenderness situated in the lower back just lateral to the spinal process in the paravertebral region. Moreover, a fingertip small point of maximum pain may be present within this painful area. Upper body bending or lateroflexion might elicit a recognizable pain. At this tender area, skin sensation is disturbed (hypo- or hyperesthesia, altered cold perception) when tested using a gently touching swab and an alcohol soaked gauze. A positive pinch test at the site of maximal pain is often present[24,26]. Additional blood tests and imaging are consistently normal. If these criteria are present, a diagnostic injection at the maximum pain point should be offered. A (temporary) response to a local diagnostic tender point infiltration using lidocaine contributes to a presumed diagnosis POCNES.

In the present case-series, 2 to 5 ml of local anesthetics were administered, depending on patient's weight and/or subcutaneous thickness around the tender point. We are aware that in the field of anesthesiology even smaller volumes of local anesthetic agents for peripheral nerve blockade may be preferred. It also has been shown that larger volumes may lead to increased rates of adverse events[40]. Furthermore, uncontrolled spreading of relatively large volumes of local anesthetic agents may reduce diagnostic specificity[41,42]. A possible option would include local electrical nerve stimulation under ultrasound guidance as performed with PRF, since this approach may allow for a more appropriate identification of the affected nerve. Using a closed electrical circuit, proper localization of the nerve is achieved by sensory stimulation. Sensations

such as paresthesia, numbness or the recognizable pain should occur at less than 0.5 Volts if the needle's position is correct[43]. This technique was not used in the presented case series but may potentially diminish low volumes of local anesthetics for diagnostic nerve blockades as also observed in ACNES patients[44]. In our series, 11 of 14 patients reported a temporary pain relief of days to weeks after the diagnostic injection. Although possibly different from what may be observed in ACNES patients, limited short-term efficacy of injection therapy in POCNES justified a surgical neurectomy once debilitating pain symptoms persist.

The differential diagnosis of POCNES is extensive and includes thoracic radicular pain, thoracic facet pain and the thoracolumbar syndrome (TLS, also known as Maigne's syndrome)[6,7,45]. Thoracic radicular pain is characterized by a locoregional pain that radiates into a specific dermatome[7]. In contrast, patients with thoracic facet pain may present with a variety of symptoms including unilateral and/or bilateral low back pain, tenderness of zygapophysial joints (facet) or transverse processes upon palpation, and pain that aggravated with lateral flexion and/or rotation[46,47]. This diagnosis of facet pain should be considered if patients report paravertebral pain that worsens by prolonged standing, extending or rotating the spinal column. Pain is usually radiating into a somewhat larger area whereas specific point of maximum pain is absent. Moreover, the pain concerns overlapping multiple dermatomes[7]. As in POCNES, the diagnosis is usually established by local anesthetic blocks[7].

Alternatively, the thoracolumbar syndrome (TLS) is defined as a localized thoracolumbar backache caused by irritation of the facet joints resulting in pain that irradiates towards the iliac crest area corresponding with cutaneous branches of T12 to L2[6]. The associated back pain is occasionally accompanied by sensory disturbances and trigger points that are almost solely situated over the iliac crest, usually at least 7 or 8 cm away from the midline[48,49]. The anatomical pattern of innervation explains why pain arising from facet joints projects itself as referred pain around the iliac crest. This theory can also be reversed with a local entrapment neuropathy at the osteofibrous tunnel near the iliac crest in fact reflecting irritation of facet joints localized higher up. It may be argued that the diagnoses POCNES and TLS share certain symptoms. However, POCNES is caused by entrapment of lateral branches of the dorsal ramus of T7 to T12 whereas TLS emanates only from T12 to L2 and refers to the superior clunial nerves[45]. In addition, the maximum pain site in POCNES is located just (3-5 cm) lateral to the spinal process in the paravertebral region instead of more laterally at the iliac crest as in TLS. Therefore, POCNES is hypothesized to be a new clinical entity due to its specific nature and distribution pattern.

The present case series does not allow for a speculation on the nature of risk factors. However, 6 of 14 POCNES patients had previously undergone an anterior neurectomy for ipsilateral ACNES. Time between the first onset of ACNES and the diagnosis of POCNES in these cases was 12 months (median, range 8-32). If entrapment of an intercostal nerve occurs, the most distal portion (anterior) is preferentially at risk[19]. However, nerve lesions may cause molecular changes in nociceptive neurons (C-fibres) and non-nociceptive neurons (Aδ- or

Aβ-fibres) by releasing growth factors[50]. These growth factors can result in hyperexcitability of initially normal surrounding nerves. This dynamic process could also spread towards more proximal portions of the originally affected nerve lesion[51]. It is hypothesized that this mechanism could lead to 'irritation' along the entire anatomical nerve tract and thereby even affect the posterior rami of the thoracic nerve. Indeed, substantial numbers of ACNES patients having anterior abdominal pain report, flank or even back pain reflecting involvement of more proximal portions of the thoracic spinal nerve (Mol et al, Department of Surgery, Máxima Medical Center, unpublished data, December 2018[52]). Unfortunately, data on earlier tests of back pain in these six ACNES patients were not obtained. Nevertheless, the present findings suggest that each patient with intercostal neuralgia should undergo an examination of the abdomen, flank as well as lower back to determine the presence of somatosensory disturbances and specific tender points along the entire thoracic spinal nerve.

This current study harbors flaws including its retrospective character and a limited number of patients who were analyzed in two tertiary referral centers precluding generalizability. As tertiary referral centers for abdominal wall related pain, results may not immediately be extrapolated to an average clinical practice due to potential referral and selection bias such as by indication. As a consequence, this novel syndrome may only be diagnosed in a small number of patients having spinal pain. However, this paper contributes to the awareness and possible treatment of patients who would otherwise remain burdened by their pain. It is also appreciated that tests such as laser evoked potentials, nerve biopsies, Quantitative Sensory Testing objectively determining somatosensory disturbances were not used[14]. Nevertheless, we feel confident that our patients were having characteristic signs and symptoms associated with affected posterior branches of thoracic nerves as also reported in similar syndromes such as ACNES and LACNES[24,25]. Our conviction is strengthened by the observation that seven of eleven patients receiving a local neurectomy of the posterior cutaneous nerve branch reported a complete and long lasting pain relief.

In conclusion, a posterior cutaneous nerve entrapment syndrome (POCNES) should be considered in patients with chronic localized back pain. Specifics in the patient's history and simple bedside tools may aid in determining whether the pain is related to entrapment of cutaneous branches of posterior rami of the thoracic nerves. A treatment regimen including injections and neurectomy may offer long term pain relief in over half of these patients.

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CHAPTER 8

Lateral cutaneous nerve entrapment syndrome (LACNES): A previously unrecognized cause of intractable flank pain

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ABSTRACT

Background and aims: Chronic abdominal pain may occasionally be due to terminal endings of intercostal nerves (ACNES, abdominal cutaneous nerve entrapment syndrome) that are entrapped in the abdominal wall. Spontaneous neuropathic flank pain may also be caused by involvement of branches of these intercostal nerves. Aim is to describe a series of patients with flank pain due to nerve entrapment and to increase awareness for an unknown condition coined Lateral Cutaneous Nerve Entrapment Syndrome (LACNES).

Methods: Patients possibly having LACNES (constant area of flank tenderness, small point of maximal pain with neuropathic characteristics, locoregional altered skin sensation) presenting between January 2007 and May 2016 received a diagnostic 5-10 mL 1% lidocaine injection. Pain levels were recorded using a numerical rating scale (0, no pain to 10, worst possible). A >50% pain reduction was defined as success. Long term effect of injections and alternative therapies were determined using a satisfaction scale (1, very satisfied, no pain - 5, pain worse).

Results: 30 patients (21 women, median age 52, range 13-78) were diagnosed with LACNES. Pain following one injection dropped from 6.9±1.4 to 2.4±1.9 (mean, $P < 0.001$) leading to an 83% immediate success rate. Repeated injection therapy was successful in 16 (pain free n=7, pain acceptable, n=9; median 42 months follow-up). The remaining 14 patients received (minimally invasive) surgery (n=5) or other treatments (medication, manual therapy or pulsed radiofrequency, n=9). Overall treatment satisfaction (scale 1 or 2) was attained in 79%.

Conclusions and implications: LACNES should be considered in patients with chronic flank pain. Injection therapy is long term effective in more than half of the population.

INTRODUCTION

Flank pain may be defined as a sensation of discomfort that is located in the area between the axilla and iliac bone. Patients with acute flank pain often suffer from an underlying visceral disease such as gallbladder stones or kidney disease. However, chronic flank pain in patients with normal blood and urine tests and normal imaging is a diagnostic challenge for general physicians and medical specialists.

The department of General Surgery/SolviMáx has gained ample experience in the treatment of chronic abdominal pain or groin pain of various causes[1-3]. A large portion of these painful patients are found to suffer from a neuropathic pain syndrome of anterior portions of the abdominal wall due to an anterior cutaneous nerve entrapment syndrome (ACNES)[3-6]. It was our impression that a subset of patients who were referred for possible ACNES actually presented with a lateral variant of an ACNES-like pain entity. These individuals reported a neuropathic pain that mimicked ACNES, although the location was far more laterally located in the flank region. As far as we know, only two cases of "entrapped" lateral branches of intercostal thoracic nerves causing flank pain have previously been reported by others[7,8].

The abdominal wall including the flank region is sensory innervated by anterior and lateral cutaneous branches of 6 paired thoracic intercostal nerves (T7-12)[9,10]. Anterior cutaneous nerve entrapment syndrome (ACNES) is a condition in which terminal (abdominal) parts of these cutaneous intercostal nerve branches are traumatized or triggered by a hitherto unidentified event leading to a local abdominal pain syndrome presenting in the area of the rectus abdominal muscle[9]. Specific ACNES characteristics include a small area (several square centimeters) of maximum pain, altered skin sensation covering this tender point, a positive pinch test and a positive Carnett's test (increased local tenderness by tensing the abdominal muscles)[2,11]. Recently, a novel variant of ACNES was coined Posterior Cutaneous Nerve Entrapment Syndrome (POCNES). This POCNES syndrome is associated with severe localized (lower) back pain, and it was found that posterior branches of the intercostal nerve were entrapped in the region of the thoracolumbar muscle group[12].

The lateral cutaneous branches of an intercostal nerve pass the external intercostal muscles and the serratus anterior muscle towards the flank area. While piercing through these muscles they divide into an anterior and posterior branch (Figure 8.1). This piercing site is possibly a preferred location of entrapment of this part of the nerve leading to a typical neuropathic flank pain that we propose to coin lateral cutaneous nerve entrapment syndrome (LACNES). Aim of the present study is to describe a case series of patients who were diagnosed and treated for possible entrapment of lateral branches of intercostal nerves, seen at our institution over the past 10 years.

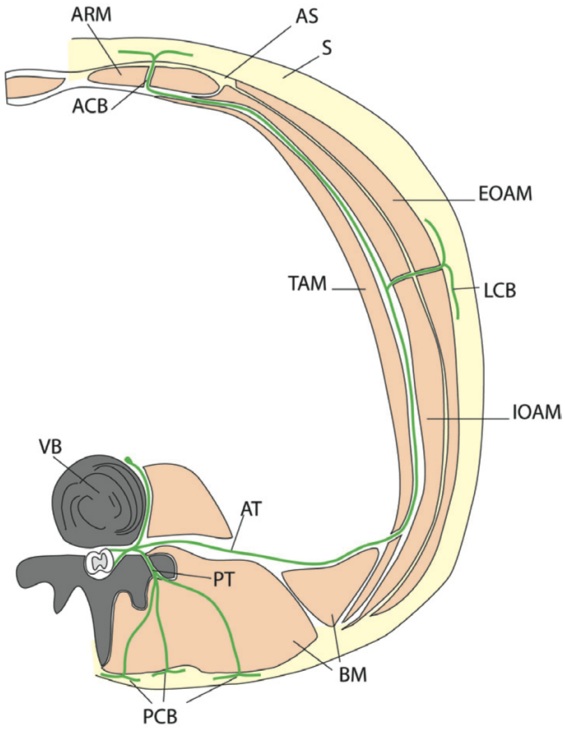

Figure 8.1:

Anatomy of intercostal cutaneous nerve branch originating from the spinal cord with posterior (PCB), lateral (LCB) and anterior branches (ACB).

VB vertebrae, RAM rectus abdominis muscle, EOAM external oblique abdominal muscle, IOAM internal oblique abdominis muscle, TAM transverse abdominal muscle.

METHODS

The present study retrospectively evaluated patients who were analyzed for chronic abdominal wall pain between January 2007 and May 2016 in the department of General Surgery/SolviMáx, Máxima Medical Center, the Netherlands, a 631-bed teaching hospital. The ethics committee of our hospital approved the study protocol (N17.009). The present study follows guidelines of the declaration of Helsinki (version October 19th, 2013). This manuscript adheres to the applicable STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines[13]. In addition to the present case series, one illustrative patient is reported in greater detail with the clinical picture, pathology findings and intraoperative images to further support the proposed hypothesis of an alleged 'entrapment neuropathy' leading to localized neuropathic flank pain.

Patient selection and inclusion criteria

Surgeons of our hospital have a special interest in patients with chronic abdominal wall pain and groin pain. Outpatient department activities are performed in a center of expertise (Solvimáx). During the study period, the majority of LACNES patients was identified from a large population of patients presenting to SolviMáx with abdominal pain of unknown origin by two senior authors using a standard history and physical examination[4]. A subset of LACNES patients was diagnosed by one of these senior surgeons at a regular surgical outpatient clinic, occasionally as a follow-up after abnormal visceral imaging.

Physical examination includes a series of standard tests. The patient is asked to indicate the location of maximum pain. A cotton swab and alcohol soaked gauze are used to evaluate skin gnostic and vital sensibility covering this tender point. Somatosensory disturbances such as hypoesthesia, hyperesthesia, allodynia or altered cool perception are commonly found as compared to the contralateral flank. Furthermore, pinching the skin is often extremely painful compared to the opposite non-involved side (a positive Pinch test).

Inclusion criteria for the diagnosis LACNES are based on an extensive (but entirely subjective) experience in patients with ACNES[2,4]. Patients were eligible for inclusion if at least 3 out of 4 of the following criteria were met:

1) A >3 month history of locoregional flank pain
2) A constant area of tenderness located in the flank covering a fingertip small point of maximal pain in the midaxillary line (Figure 8.2)
3) A larger area of altered skin sensation such as hypoesthesia, hyperesthesia or altered cool perception covering this maximal pain point, but not necessarily corresponding to a specific complete dermatome
4) A positive Pinch test (using thumb and index finger to 'pinch' and lift the skin around the tender point eliciting a painful response in comparison to the contralateral side)

Normal laboratory testing and imaging (ultrasonography, computed tomography) contributed to consideration of the diagnosis LACNES, but was not required per se. Exclusion criteria were surgical scar–related pain syndromes, thoracolumbar disease or impaired communication.

If diagnostic criteria were satisfied, the presumptive diagnosis LACNES was communicated to the patient and specifics of a diagnostic injection procedure were explained. Following verbal consent, 5-10 mL of 1% lidocaine was administered as follows. The exact amount of administered anesthetic agent was based on the presumed weight of patients and/or the estimated thickness of subcutis covering the tender point. The patient was asked to sit or stand with a raised ipsilateral arm. After skin disinfection, the point of maximal pain was marked with a pencil. A 21 G 40 mm needle was used to administer the lidocaine. Needle tip placement was done 1 to 2 cm below the fascia of the external oblique muscle or serratus muscle, in proximity to the tender point using a free hand technique (Figure 8.3).

Figure 8.2:

A patient with LACNES.

The point of maximal pain (swab) is located in the right midaxillary line that is covered by an area of altered skin sensation (////, hyperesthesia, altered cool perception and positive pinch test. (Photos with permission)

Figure 8.3:

Free hand tender point-infiltration using 1% lidocaine combined with 40 mg of methylprednisolone.

Data accrual and outcome measurements

Pain was measured on a numerical rating scale [NRS, 0 (no pain) to 10 (worst possible pain)] immediately before and some 10-15 minutes after the injection. If levels of pain were considerably lower (e.g. >50% pain reduction), characteristics of the diagnosis were again communicated, and the patient received a control appointment after 2-3 weeks. If the pain had recurred by then, a combination of 5 ml of 1% lidocaine and 40 mg of methylprednisolone was injected. If levels of pain after this regimen remained unacceptable or if patients declined ongoing injection therapy, they were either referred to a pain clinic for alternative treatments such as medication, physical therapy, manual therapy or pulsed radiofrequency therapy (PRF) or treatment of a visceral source (if present) was performed. A hospital electronic search using a diagnosis code exclusively assigned to abdominal wall related pain syndromes was performed for identification of potential patients. All records were consequently identified hand searched to identify individuals suspected of having a neuropathic pain syndrome in the flank. Specifics including age, gender, body mass index, diagnostic delay, etiology and NRS scores (if present) at baseline and time of follow-up.

A final follow-up evaluation was performed by the first author (RM) in July and August 2016 by phone assessing long-term clinical success and level of satisfaction as previously published (verbal rating scale, VRS, Table 8.1)[4]. Clinical success was defined as VRS 1-2 ([very] satisfied), while a VRS of 3 was defined as an attenuation of pain levels. The therapy had failed if a VRS 4-5 was reported.

Table 8.1:
Level of satisfaction after treatment for ACNES using Verbal Rating Scale*.

1	I am very satisfied; I have no pain anymore.
2	I am satisfied; I occasionally experience some pain.
3	I have improved, but experience some pain on a regular basis.
4	The treatment did not change my pain level.
5	My pain has worsened after the treatment.

Reproduced from Boelens OB, Scheltinga MR, Houterman S, Roumen RM. Management of anterior cutaneous nerve entrapment syndrome in a cohort of 139 patients. Ann Surg. 2011;254(6):1054–1058.24[17]. Abbreviation: ACNES, anterior cutaneous nerve entrapment syndrome.

Data analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21 for Windows. Categorical variables were described as frequencies. Continuous data were tested for normality and are presented as means with standard deviation (±SD) or median values (range) as appropriate. Changes in pain scores after lidocaine infiltration were evaluated using paired T-testing. A p-value of <0.05 was considered significant.

RESULTS

Baseline patient characteristics

Thirty patients evaluated in MMC's Department of General Surgery and SolviMáx retrospectively fulfilled inclusion criteria of LACNES during the almost 10 year study period. Characteristics are listed in Table 8.2. There were 21 (70%) females and 9 (30%) males. Median age was 52 years (range, 13 – 78). Patients were referred after a median 18 months (range, 3-360), indicating the long duration of this pain entity. Flank pain was more often located on the right than on the left side (80%, 24/30 vs 20%, 6/30). A positive skin pinch test was detected in 90% (27/30). All 30 patients had undergone imaging (e.g. US, CT or MRI scan) to exclude organic disease. Interestingly, underlying visceral abnormalities were demonstrated in nine (liver adenoma (n=2), liver cyst (n=3), a spontaneous/congenital intrahepatic porto-caval shunt (n=1); splenic cyst (n=1) and kidney cyst (n=1) and multiple gallstones (n=1). An expectative policy was used in the patients with liver cysts, porto-caval shunt and gallstones.

Table 8.2:
Characteristics of patients with lateral cutaneous nerve entrapment syndrome (LACNES).

	LACNES (n = 30)
Age (range)	52 (13 – 78)
Gender, F:M ratio	21 : 9
Body mass index, kg/m^2 (SD)	23.7 (5.1)
Diagnostic delay, months (range)	18 (3 – 360)
Etiology (n)	
Spontaneous	21
Previous abdominal surgery	8
Sports	1
Local sensory dysfunction covering pain point	24
Pain level at presentation (NRS, 0-10)	6.9 (1.4)

Data are presented as mean with standard deviation (± SD), or median values with ranges. NRS, Numerical Rating Scale.

Diagnostic and therapeutic injections for LACNES

Interventions for LACNES are depicted in Table 8.3. All patients consented to a diagnostic maximal pain point lidocaine infiltration. In these 30 patients, mean pre- and post- NRS scores were found to drop from 6.9±1.4 to 2.4±1.9 ($p < 0.001$). Twenty five (83%) reported a >50% pain reduction following the diagnostic injection (Figure 8.4).

After this single diagnostic injection, 5 of the injected 30 patients (17%) were pain-free in the short term (median one month) as well as in the long term (median 60 months, range 2-103). Two additional patients were long term pain-free after 1-3 repeated injections (respectively 36 and 55 months FU). Thus, 7 of 30 (23%) were long term pain free by an injection regimen only (VRS =1). Another nine patients reported substantial pain relief in the short term and opted for incidentally repeated injections, if required. Pain levels in this subset were acceptable in the long term (median 24 months, range 2-52; VRS =2). As a consequence, the overall long term injection therapy success rate was 53% (16/30). Two patients received manual therapy simultaneously with injection therapy but they attributed pain relief to injections rather than to manual therapy. One patient who had short-term success with injection therapy experienced a recurrence of pain and was referred to a manual therapist leading to attenuated pain levels (VRS 3).

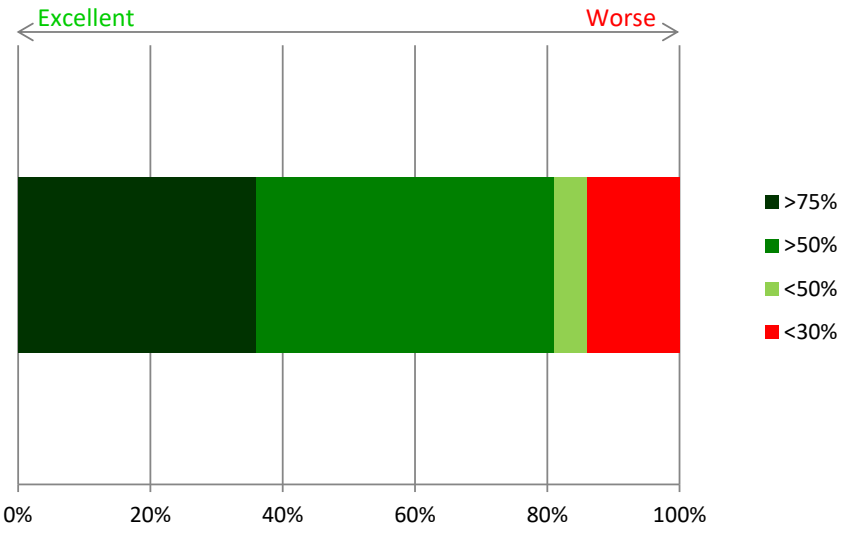

Figure 8.4:
Pain reduction before and after a diagnostic injection in LACNES.

Alternative therapies for LACNES

Of the fourteen patients who did not successfully respond to injection therapy, six were referred to a pain service for medication or pulsed radiofrequency therapy (PRF) which led to acceptable pain levels in two (VRS 2). The other four still had residual pain at the final evaluation. Three other patients were referred to a manual therapist, with one achieving acceptable results (VRS 2).

Table 8.3:
Characteristics and Success of Interventions in LACNES patients (n=30).

	Patient characteristics			Dx Injection	
Pt	Age	Location	Pain area in corresponding dermatome	NRS pre	NRS post
1	72	Right	Th10	-	-
2	57	Right	Th10	7	0
3	50	Right	Th9	9	4
4	51	Right	Th9	4	0
5	42	Right	Th8	4	0
6	13	Left	Th9	-	-
7	66	Right	Th9	5	0
8	50	Right	Th11	6	2
9	46	Right	Th11	-	-
10	52	Left	Th10	8	4
11	32	Right	Th9	8	3
12	71	Right	Th7	-	-
13	78	Right	Th11	5	3
14	55	Right	Th12	7	3
15	26	Left	Th7	8	2
16	71	Right	Th9	8	0
17	58	Right	Th8	7	3
18	48	Right	Th9	6	5
19	59	Right	Th9	9	4
20	48	Left	Th8	8	0
21	54	Right	Th9	7	3
22	64	Right	Th11	6	2
23	23	Right	Th7	8	3
24	47	Left	Th11	-	-
25	55	Left	Th7	6	0
26	52	Right	Th10	7	5
27	52	Right	Th8	8	6
28	68	Right	Th11	8	4
29	30	Right	Th11	-	-
30†	61	Right	Th8	-	-

*Dx diagnostic, IT injection therapy, MT manual therapy, PS pain specialist, NRS Numerical Rating Scale pre / post injection. - Missing data * Success injection therapy is defined as >50 % reduction of pain during >6 weeks, #Long term success at FU is defined as attaining final VRS 1 or 2 (corresponding with >50% pain reduction, n = 23) after receiving one or more interventions. † patient passed away before final follow-up.*

Treatment					Follow-up	
Number of injections	MT	PS	Treatment visceral source	Neurectomy	Success IT*	Final VRS#
1					Yes	1
1					Yes	1
4					Yes	1
3					Yes	2
1	X				Yes	1
1	X				Yes	2
3		X			No	2
1		X			No	2
1					Yes	1
1	X				No	2
2					Yes	1
3					Yes	2
3					Yes	2
4			X		No	1
1			X		No	1
3					Yes	2
2			X		Yes	1
2					No	2
5					Yes	2
1					Yes	1
1					Yes	2
2					Yes	2
2				X	No	2
1		X			No	4
4	X				No	3
1		X			No	4
2	X				No	4
2		X			No	4
1			X		No	4
1		X			No	†

Surgery was performed in the 5 remaining patients. Drainage of a spleen cyst (n=1) and kidney cyst (n=1) as well as embolization of a liver adenoma (n=1) cured the neuropathic flank pain in all three. The fourth patient was referred to an academic hospital for embolization of liver adenoma but the pain remained (VRS 4). Therefore, visceral treatment had a 75% success rate (3/4; VRS 1-2). One patient receiving a neurectomy is described in more detail as follows

Case report

A 23-year old female presented with an 18 month history of flank pain located at the right mid-axillary region. Her complaints had presented spontaneously and were slowly progressive leading to a continuous stabbing pain that was provoked by physical effort. Diagnostics and treatments by an orthopedic surgeon and a neurologist were to no avail. She also received TENS treatment, PRF treatment and cryoneuro ablation by a pain specialist but also without relief. Analysis by this pain specialist showed a DN4 (Douleur Neuropathique 4) score of 5, suggesting a neuropathic character of her pain symptoms. Physical examination revealed a constant area of hypoesthesia of approximately 5x5cm overlying a small point of maximum pain located at the anterior axillary line at the level of the right seventh rib. Two Ultrasound guided infiltrations using local anesthetics had a beneficial albeit temporary response. Following an extensive consultation, a local surgical exploration was proposed and consented. Prior to operation, the area of interest was marked onto the skin. Once general anesthesia was administered, the sheath of muscle or serratus anterior was exposed via a transverse 7-cm skin incision. The neurovascular bundle was identified. The fascia was widened and this bundle and its branches were tracked down until it reached the caudal border of the rib edge and was consequently coagulated and removed (Figure 8.5). Accompanying vascular structures were ligated or also coagulated. The sheath and the remainder of the wound were closed in layers using absorbable suturing material. Pathological analysis revealed normal nerve tissue. The patient was pain free at the 6 weeks postoperative outpatient control and remained up to the last control (6 months follow up).

Long term treatment satisfaction

A 100% response rate was attained after a median 40 months follow-up in the surviving 29 patients (range 2 – 103). One patient died of unrelated cause. More than three quarters (79%, 23 of 29) were satisfied with the therapeutic result (VRS 1-2). One patient (4%) reported improvement but regularly experienced pain (VRS 3). Therapy was unsuccessful in the five remaining patients (17%, VRS 4). No VRS 5 was scored.

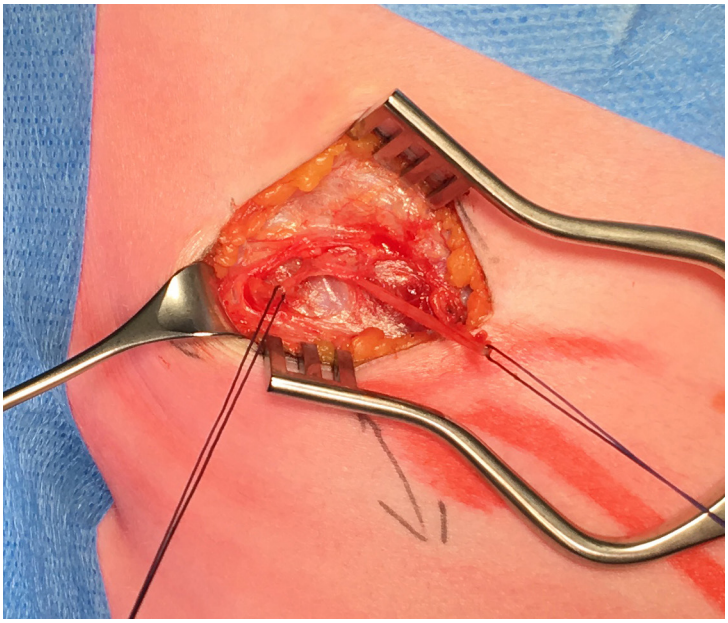

Figure 8.5:

Intraoperative view of a neurovascular bundle (loop) and a nearby branch (loop) perforating the fascia of the serratus muscle.

Point of view: inframammary on the right side of the supine patient. Black arrow pointing caudally showing the irradiation route of pain that was described by the patient.

DISCUSSION

The present retrospective case series found that a small portion of patients who were referred to a tertiary referral center for evaluation of a chronic abdominal pain syndrome were found to suffer from (possible) neuropathic pain in the flank. These patients demonstrated pain characteristics resembling ACNES although the point of maximal pain was situated far more laterally[4]. Aim of the present study was to describe a series of these patients who were diagnosed and treated for a possible entrapment of intercostal flank nerves. The most important finding is that this novel syndrome should be considered in the differential diagnosis of chronic flank pain. Injection therapy using a combination of local anesthetic agents with or without steroids appeared long term effective in a little over half (53%) of the population. We propose to coin this syndrome lateral cutaneous nerve entrapment syndrome (LACNES).

It may well be that the set of symptoms of the present cases who are labelled as LACNES was previously described by others using different terminology. In the available literature, one case report was found describing a lateral cutaneous nerve entrapment syndrome[7]. Another case

report described a case of ACNES although the pain actually was located more laterally in the flank[8]. More recently, a posterior version of ACNES was identified suggesting involvement of posterior branches of cutaneous intercostal nerves at the lower back[12]. The present study is the first case series reporting on specific features of entrapment of lateral branches of intercostal nerves that also discusses diagnostic and treatment protocols.

If one proposes a novel syndrome, a clear set of criteria is needed. All patients demonstrated a clinical picture that was characterized by a constant site of lateral abdominal tenderness located in the flank (mid axillary region between the costal arc and the iliac crest) with a fingertip small tender point (Figure 8.2). Moreover, most (90%) had a positive pinch test defined as a disproportionally intense pain following skin pinching using thumb and index finger compared to the opposite flank. Similar to ACNES, the pain is accompanied by skin somatosensory disturbances (hypoesthesia, hyperesthesia, hyperalgesia and altered cool perception) that is limited to a discrete area in the flank, indicating some kind of local nerve involvement. In each future patient fulfilling these criteria, the presumptive diagnosis of LACNES should be considered and a diagnostic injection should be offered.

Abdominal cutaneous nerve entrapment syndrome is considered as an "entrapment" neuropathy of cutaneous branches of the 7-12th intercostal nerves[9]. Neuropathic pain has been defined by the International Association for the Study of Pain (IASP) as pain caused by a (demonstrable) lesion or disease of the somatosensory nervous system[14]. A local neurectomy of the lateral cutaneous nerve branch in one patient resulted in complete and long lasting pain relief. A tissue analysis demonstrated normal nervous tissue. This finding supports the hypothesis that entrapment of cutaneous branches of intercostal nerves may possibly lead to a severe neuropathic flank pain entity.

It is remarkable that treatment of a visceral entity cured the neuropathic flank pain in 3 of 4 LACNES patients having parenchymal disease including liver, kidney and spleen. It is thought that a segmental relation between a visceral abnormality and the abdominal wall may explain somatosensory abnormalities and neuropathic pain of the latter. Such connections were described already more than one century ago by Head ("Head zones") and MacKenzie[15,16]. MacKenzie proposed the term 'referred pain' that was defined as pain originating from internal organs that is projected onto a predictable skin area. Relevant to this discussion is an often cited theory that hypothesizes the presence of viscerocutaneous reflexes. Visceral afferent nerve fibers converge with cutaneous pain afferents at the level of the dorsal root ganglion and spinal cord[15-17]. Higher brain centers are possibly not able to distinguish neuropathic abdominal wall pain from visceral pain. One of the senior authors (RR) is also a liver surgeon skilled in the treatment of a range of liver pathologies. His subspecialty has likely contributed to the identification of neuropathic pain symptoms located in the right upper midaxillary line. The somewhat peculiar combination of visceral abnormalities and coinciding neuropathic pain strongly supports the presence of these segmental relations that modern-day clinical medicine, with its focus on high tech imaging, tends to ignore.

Most patients in our study were referred after a median of more than one and a half year diagnostic delay suggesting that this lateral variant is also frequently overlooked as a cause of chronic flank pain as also has been observed in other types of chronic abdominal wall pain[18-20]. However, there exist some differences between the abdominal myofascial pain syndrome (AMPS) and ACNES[20-23]. Contrary to ACNES, skin pinching in AMPS is usually normal, as is the local skin sensibility covering the painful area. Moreover, gender distribution is almost equal (females : males = 54:46)[22]. It is thus unlikely that the beneficial effect of the local injections can be seen as placebo effect. It is hoped that the present study contributes to an earlier recognition of patients with LACNES.

This study obviously harbors flaws including its retrospective character. It describes a patient series with a relatively small volume that is collected over a 10 years period by a selected group of clinicians. Referral bias is present due to the nature of our institution. Different types of treatment were proposed due to lack of knowledge in the early years of this case series. A standardized treatment regimen should prospectively be evaluated in future studies of flank pain. Furthermore, the diagnosis LACNES was not demonstrated by objective tests that are associated with somatosensory disturbances including laser evoked potentials, nerve biopsies (except the single operative case), Quantitative Sensory Testing or MRI imaging[24]. We also did not standardly use specific questionnaires suggesting neuropathic pain, like DN-4, LANSS, Pain DETECT, or the Neuropathic Pain Syndrome Inventory[24]. Nevertheless we feel confident that the patients presented in this series were having neuropathic pain due to affected branches of intercostal nerves as also reported in similar syndromes such as ACNES and POCNES[4,12]. We are currently considering wider deployment of performing a neurectomy of the affected nerve as was done in the presented case, and as has previously been described in patients with recalcitrant ACNES[2,25].

In conclusion, lateral cutaneous nerve entrapment (LACNES) should be considered in the differential diagnosis of chronic flank pain. Injection therapy using a combination of local anesthetic agents with or without steroids is long term effective in over half of this population. Further research is needed to establish a standardized treatment protocol and investigate the effect of a local surgical exploration in treating LACNES patients

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CHAPTER 9

Bilateral distribution of anterior cutaneous nerve entrapment syndrome (ACNES): Are clinical features and outcomes comparable to unilateral ACNES?

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ABSTRACT

Background and objectives: Mirror-image pain may occur in the presence of a one-sided peripheral nerve lesion leading to a similar distribution of pain on the contralateral side of the body ('mirrored'). Anterior cutaneous nerve entrapment syndrome (ACNES) is a neuropathic pain syndrome due to entrapment of terminal branches of intercostal nerves T7-12 in the abdominal wall and sometimes presents bilaterally. This study aims to address specifics of bilateral ACNES and to determine potential differences in clinics and outcome when compared to the unilateral form of ACNES.

Methods: Electronic patient files and questionnaires of a case series of patients who were evaluated for chronic abdominal wall pain in a single center were analyzed using standard statistical methods.

Results: Between June 1st, 2011 and September 1st, 2016, 1116 patients were diagnosed with ACNES, of which a total of 146 (13%) with bilateral ACNES were identified (female, n=114, 78%; median [range] age 36 [11-81] yrs). Average NRS (Numeric Rating Scale; 0-10) scores were similar (median [range] NRS scores 6 [0-10] although peak NRS scores were significantly higher in the bilateral group (9 [5-10] *vs*. 8 [2-10]; p=0.02). After a median of 26 months [1-68], the proportion of bilateral ACNES patients reporting treatment success was 61%.

Conclusions: One in eight ACNES patients has bilateral abdominal wall pain. Characteristics are similar to unilateral ACNES cases. Further studies aimed at underlying mechanisms in mirror image pain pathogenesis could provide a more targeted approach in the management of this neuropathic pain.

INTRODUCTION

Chronic abdominal pain (CAP) is usually attributed to diseases of internal organs[1]. However, in up to 30% of CAP patients pain is found to originate from the abdominal wall rather than from a viscus[2]. CAP in these individuals often results from anterior cutaneous nerve entrapment syndrome (ACNES) although this diagnosis is frequently not considered[3]. Wrongfully attributing CAP to intra-abdominal disorders could lead to unnecessary consultations, testing, and even futile abdominal surgery.

Considering the neuroanatomy of the abdominal wall may facilitate the understanding of the pathology of ACNES. The abdominal wall is sensory innervated by anterior and lateral cutaneous branches of anterior rami of the thoracic intercostal nerves (7^{th}-12^{th})[4]. It was theorized that *anterior* intercostal nerve branches at ventral portions of the abdomen are triggered by an unknown pathophysiological event leading to a local anterior abdominal pain syndrome in the area of the rectus abdominal muscle[4]. Specific ACNES characteristics include a small area (several square centimeters) of maximal pain, altered skin sensation covering this tender point, a positive Pinch test and a positive Carnett's test (increased local tenderness by tensing the abdominal muscles)[1]. Recent studies demonstrated that lateral and posterior cutaneous branches are also able to generate neuropathic flank and back pain syndromes mimicking ACNES[5,6].

Unpublished data from our institution regarding a large cohort encompassing 1116 patients diagnosed with ACNES showed that 13% presented with a bilateral pain syndrome. It is our experience that bilateral cases most often have pain at an identical dermatome level: 'mirrored' (e.g. bilateral T10: right and left at umbilical level). It is thought that a complex underlying mechanism of 'communicating' neural pathways may occasionally result in bilateral pain. Aim of our study is to report on specifics of this complex subtype of ACNES. Unique findings at physical examination, pathophysiologic mechanisms and treatment results of this subdivision of ACNES patients are discussed.

METHODS

Setting

A retrospective cohort study was performed between November, 2017 and February, 2018 in the Department of General Surgery of Máxima Medical Centre (MMC), The Netherlands. This study analyzed data from consecutive patients who were referred for a potential abdominal wall pain or groin pain syndrome to the SolviMáx Center of Excellence for Abdominal Wall and Groin Pain, Eindhoven, between June 1st, 2011 and September 1st, 2016. All patients provided signed informed consent forms prior to an outpatient department intake allowing for the use of anonymized patient-related outcome measures. The ethics committee of our hospital judged that results of the present study were obtained as part of an evaluation and auditing process of patient response outcome measurement (PROM). This manuscript adheres to the applicable STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Patient assessment

The presence of typical characteristics of ACNES was standardly assessed during physical examination as previously described[7]. These assessments included sensory mapping of tactile and cool sensation by using a cotton swab and an alcohol-soaked gauze to detect somatosensory disturbances of the skin covering the point(s) of maximal pain, Carnett's test (increased local tenderness by tensing the abdominal muscles) and the Pinch test (disproportional increase of pain while manually pinching an abdominal skinfold containing skin and subcutaneous tissue)[4,8]. Whenever the diagnosis of ACNES was then likely, a diagnostic injection with lidocaine was proposed. After informed consent was obtained, patients were placed supine on a stretcher. After skin disinfection, an injection of 2-5mL 1% lidocaine just underneath the anterior fascia of the rectus abdominis muscle was administered using a 21 G 40 mm needle. Volume was based on patient's weight and/or subcutaneous thickness around the tender point. Needle tip placement was just beneath the fascia of the rectus abdominis muscle, ideally into or in close proximity to the tender point using a free hand technique, as previously published for ACNES[7]. The pain was subsequently measured on a numeric rating scale [NRS, 0 (no pain) to 10 (worst possible pain)] immediately before and some 10–15 minutes after this abdominal wall injection. If levels of (spontaneous) resting pain were considerably lower and success was attained (defined as a >50% pain reduction), characteristics of the diagnosis were again communicated, and the patient received a control appointment after 2–3 weeks. If the pain had recurred by then, the patient underwent an injection regimen of repeated (1-3) local tender point infiltrations using 2-5 ml of 1% lidocaine. If levels of pain after this regimen remained unacceptable, or if patients declined ongoing injection therapy, they were either referred to a pain clinic for alternative treatments [e.g., medication, physical therapy, transcutaneous nerve stimulation (TENS), or pulsed radiofrequency therapy (PRF)], or received a surgical neurectomy procedure[7]. Treatment success was defined as > 50% pain reduction on the NRS. Results of the neurectomy procedure are scored as total (both sides), as well as per side.

Findings in ACNES patients presenting with a symmetrical bilateral pain syndrome were often as follows. A portion of patients reported pain as more diffuse rather than a small predictable localized area as observed in unilateral ACNES patients. Moreover, the location of the pain usually projected in the abdomen's midline or around the umbilical area. Most patients found it difficult to exactly determine which side was most painful. Other patients reported that pain had started at one side and extended to the contralateral side after some time. The presence of such a 'mirroring' effect was defined as exhibiting similar pain characteristics (e.g., sensory abnormalities such as hypoesthesia or allodynia) at the side opposite to the initial painful side. Sporadically, we encountered a bilateral ACNES presentation occurring at different dermatome levels (i.e., patients complaining of pain in dermatome T7 right and T10 left). This was entitled as two different ACNES tender points and not classified as mirror-image pain.

Eligibility criteria participants

Inclusion criteria consisted of **1)** a > 3-month history of abdominal pain of unknown origin, **2)** a constant area of abdominal pain, with a finger-tip point of maximum pain, located at the lateral borders of the rectus abdominis muscle at both sites of the abdomen, **3)** localized somatosensory disturbances (such as hypoesthesia, hyperesthesia and/or altered cool perception).

Exclusion criteria were: abdominal pain occurring at different dermatome levels (i.e., not symmetrical, being sporadically encountered), cognitive impairment or surgical-scar related pain syndromes.

Patients with unilateral ACNES were included as controls.

Data accrual

Characteristics of consecutive patients with an abdominal pain of unknown origin possibly having ACNES who presented to our outpatient clinic are standardly entered in the hospital's electronic patient file database. An electronic search using a diagnosis code exclusively assigned to abdominal wall-related pain syndromes was performed for identification of all ACNES patients. Possible eligible patients with a bilateral presentation of ACNES were extracted from this database and entered in a separate database for further analysis. Data of symmetrical bilateral ACNES regarding patient's assessment at the first visit, as well as data regarding, age, gender, body mass index, diagnostic delay, etiology, NRS scores, events possibly provoking the pain, time of follow-up, date of being pain-free or possible recurrences, were entered in a separate database. Patient characteristics, findings on physical examination and results of initiated treatment were compared between bilateral and unilateral cases. Coding of data was done and monitored by two independent investigators. All data were anonymized.

Literature search strategy for bilateral ACNES

Available literature on ACNES was obtained by an electronic search strategy in various databases (PubMed, MEDLINE and Embase) using the following keywords (alone or in various combinations): anterior cutaneous nerve entrapment syndrome, ACNES, chronic abdominal wall pain, chronic abdominal pain. The search strategy included studies up to December 31, 2017. Selection was based on the abstract contents whereas reference lists were screened to ensure no relevant papers were missed. Studies were eligible if they were written in English, had full text available, included detailed information on patient characteristics and specifically reported bilateral cases and were published by groups other than our institution. Data that were extracted from papers included total number of patients, number of patients with a bilateral presentation of ACNES, gender ratio, age, and study design.

Statistics

Determinants were analysed if >85% data was complete using the Statistical Package for the Social Sciences (SPSS, IBM, New York, USA) version 21 for Windows. No date imputing was performed. Categorical variables were described as frequencies. Results for continuous variables were expressed as mean (SD) or as median (range) for variables following normal and non-normal distributions, respectively. Statistical testing for non-normally distributed variables used the Mann–Whitney test, and for categorical values the χ^2 test. A p-value < 0.05 was considered significant.

RESULTS

Patient selection

Over 3000 patients were referred to our outpatient clinic between 2011 and 2016 (Figure 9.1), and 2996 were evaluated for a possible abdominal wall or groin pain syndrome. A total of 1182 patients were suspected of having ACNES whereas 1814 were excluded for reasons as depicted in Figure 9.1. Therefore, the present study is based on 1116 patients diagnosed with ACNES. In this group, 970 patients (87%) presented with unilateral ACNES and 146 patients (13%) had a bilateral ACNES. However, in 4 of these 146 patients dermatome levels which included the tender points were not symmetrically distributed and therefore excluded for further analysis.

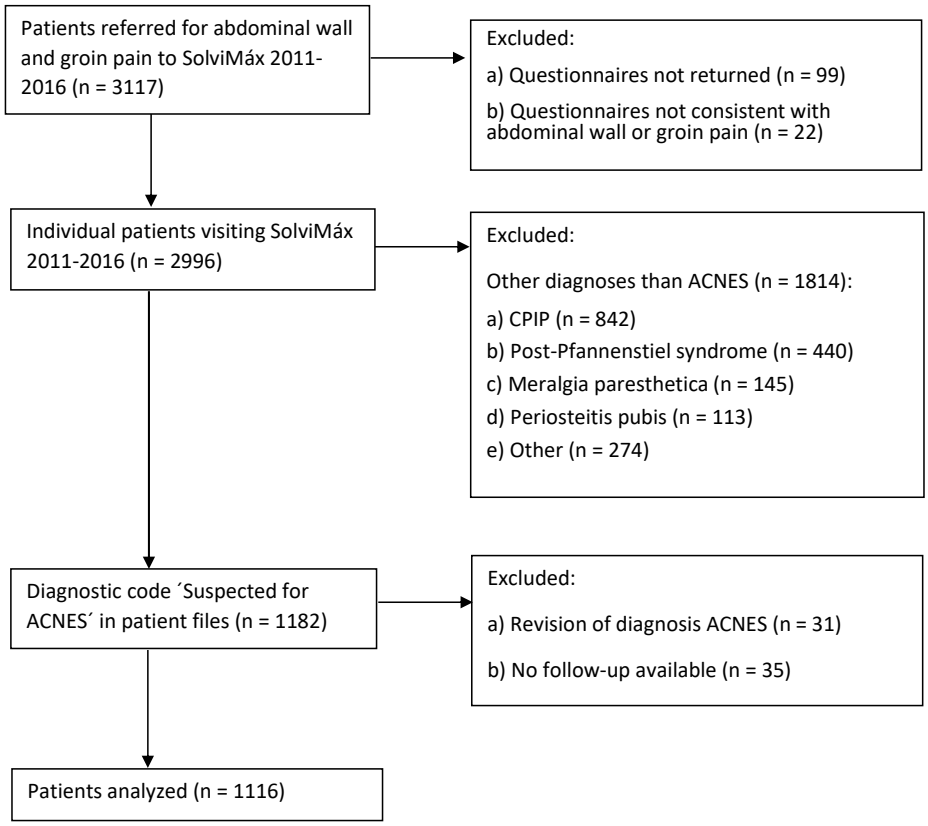

Figure 9.1:

Flow chart of ACNES patients.

Abbreviations: ACNES = Anterior Cutaneous Nerve Entrapment Syndrome; CPIP = chronic postherniorrhaphy inguinal pain.

Subject characteristics

Demographics are depicted in Table 9.1. Characteristics regarding BMI, length, weight, duration of symptoms and etiology were comparable between the two groups. However, bilateral patients (n = 142) were 8 years younger (bilateral: median age 36 [1-81] yrs *vs.* unilateral n = 970: 44 [7-81] yrs; p = 0.02). Interestingly, in unilateral ACNES patients two age peaks were observed at 16 yrs and 40 yrs, while age was distributed more equally in bilateral ACNES patients (Figure 9.2). Average NRS scores were similar although peak NRS scores were significantly higher in the bilateral group (median 9 [5-10] *vs*. 8 [2-10]; p = 0.02).

Table 9.1:
Demographics of ACNES patients presenting with a symmetrical bilateral, or with unilateral pain syndrome.

	Bilateral (n = 142)	Unilateral (n = 970)	P
Age	36 [11-81]	44 [7-81]	**0.02**
Gender, M:F, (%)	32 (23) : 110 (77)	207 (21) : 763 (79)	0.75
Height, cm	170 ± 8	169 ± 10	0.84
Weight, kg	72 ± 16	73 ± 18	0.52
BMI, kg/m²	25 ± 5	26 ± 6	0.48
Diagnostic delay, months	23 [1-624]	18 [1-528]	0.67
Etiology, %:			
Spontaneous	53%	60%	
Previous abdominal surgery	32%	27%	
Accident/sport injury	5%	5%	
Pregnancy	3%	3%	
After a flu	3%	3%	
Other	4%	2%	
NRS normal (0-10), [range]	6 (0-10)	6 (0-10)	0.24
NRS peak (0-10), [range]	9 (5-10)	8 (2-10)	**0.02**

Abbreviations: NRS = Numeric Rating Scale; IQR = interquartile range; BMI = Body Mass Index. Data are presented as medians [ranges] or means (± SD), as appropriate.

Findings on physical examination are shown in Table 9.2. Patients with bilateral ACNES presented with similar signs and symptoms on physical examination, albeit on both sides of the anterior abdominal wall. As also reported for unilateral ACNES, the majority of bilateral cases (approximately 3 of 4) presented in the lower dermatomes T10-12. A positive Pinch test *and* a positive Carnett's test was observed in 82% and 84% of bilateral ACNES patients, respectively (*vs*. unilateral, 81% and 87%, respectively).

Specifics on onset of pain symptoms in bilateral ACNES were obtained from 138/142 [97%] patients. There was a right-sided preponderance as initial starting side of complaints (right-sided n = 44 *vs*. left sided n = 31), however, the majority of patients (63/142 [44%]; p = 0.004) reported that pain symptoms started on both sides simultaneously. Remarkably, almost one-third of these patients (19/63 [30%]) reported that their pain originated in the midline and spread towards left *and* right.

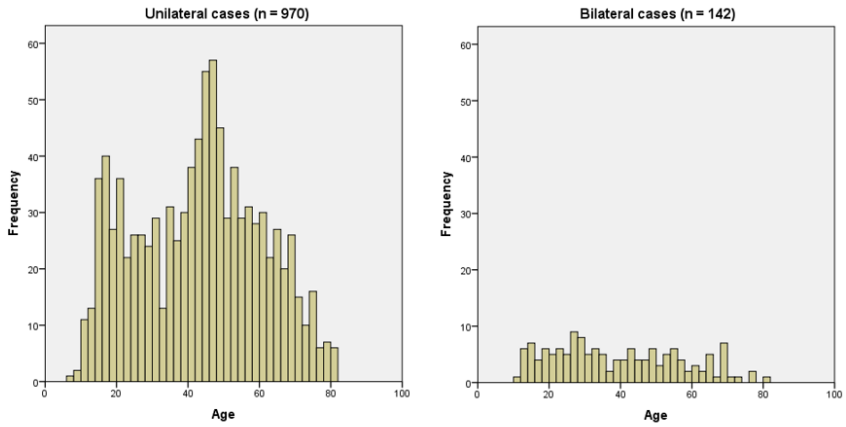

Figure 9.2:

Age of onset in unilateral and bilateral ACNES patients.

In unilateral (left) two peaks were present at around 16 and 40 years. In bilateral cases (right) patient's age was distributed more equally.

Table 9.2:
Findings in ACNES patients presenting with a symmetrical bilateral or unilateral pain syndrome.

	Bilateral (n=142)	Unilateral (n=970)	P
Abdominal wall dermatome of max. pain location			-
T7	3%	2%	
T8	10%	9%	
T9	15%	13%	
T10 (level of umbilicus)	29%	28%	
T11	27%	34%	
T12	16%	14%	
Abdominal wall side of max. pain location			-
Right	-	65%	
Left	-	35%	
Presence of local somatosensory disturbances around point of max. pain	71%	74%	0.59
- Hypoesthesia	47%	49%	
- Hyperesthesia	19%	20%	
- Allodynia	5%	5%	
Positive Pinch test	82%	81%	0.44
Positive Carnett's test	84%	87%	0.56
Presence of intercostal painful points	18%	16%	0.66
Presence of paravertebral painful points	15%	15%	0.98
Reaction modified tender point injection after 15 minutes:			
- pain free	36%	38%	0.49
- ≥ 50% pain reduction	37%	34%	0.34
- ≤ 50% pain reduction	27%	28%	0.80

Abbreviations: T = thoracic dermatomal level. Data are presented as percentages of the entire case series.

Treatment results of symmetrical bilateral cases (n = 142)

Median follow-up of the bilateral ACNES study population was 8 [1-68] months. Interventions are depicted in Figure 9.3. A total of 124 patients underwent injection therapy or/and PRF, with 28/124 [23%] patients experiencing >50% pain reduction. Eventually, 98/142 [69%] patients received a surgical intervention consisting of anterior *and* secondary posterior neurectomy when results of anterior neurectomy were insufficient.

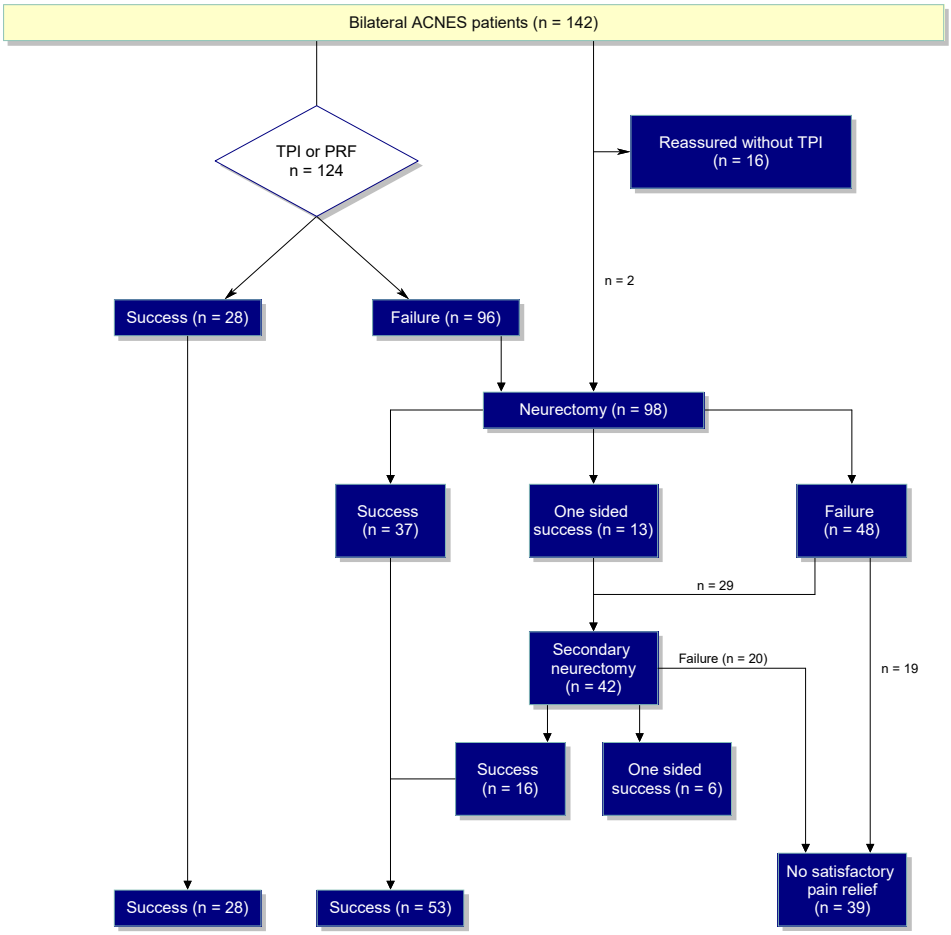

Figure 9.3:

Flowchart of 142 patients with symmetrical bilateral ACNES showing consecutive steps in the diagnosis and treatment protocol.

TPI and PRF indicate tender point infiltration and pulsed radiofrequency therapy, respectively.

After surgical intervention, complete bilateral success was attained in more than half of the patients (53/98 [54%]) with median (range) follow-up time of 13 (2-68) months. An additional 6/98 [6%] patients had >50% pain reduction at either right (n=5) or left side (n=1).

At the final follow-up visit, 87/142 [61%] of the bilateral ACNES cases reported a successful treatment result after either conservative measures such as injections, PRF or medication, or surgical intervention.

Literature search

The search strategy identified 115 papers on PubMed and 12 papers using Embase of which a total of 17 were considered eligible. Four studies were excluded since information on the exact pain location was absent[9-12]. Table 9.3 summarizes the remaining 13 studies encompassing a total of 613 ACNES patients [largest cohort included 269 patients[13]]. Most reports were case series (n = 9). A total of 62 (10.1%) bilateral cases of ACNES were identified from these reports. Numbers on the prevalence of bilateral ACNES in literature correlate well with the observed cases in our study population, which was 13%.

Table 9.3:
Authors, other than from our own institute, reporting on bilateral cases in ACNES patients.

Study	Country	No. patients	No. of bilateral cases (%)	M:F ratio[a]	Age[a]	Study design
Applegate 1972 [31]	United States	62	5 (8)	14:48	NS	Case series
Baciarello 2017 [32]	Italy	5	1 (20)	4:1	65 (34-67)	Case series
Bairdain 2015 [33]	United States	9	2 (22)	2:7	14 (10-19)	Case series
Batistaki 2013 [34]	Greece	1	1 (100)	n/a	37	Case report
Birthi 2013 [35]	United States	1	1 (100)	n/a	33	Case report
Gallegos 1989 [36]	United Kingdom	26	3 (12)	5:21	41 (19-70)	Case series
Greenbaum 1994 [37]	United States	56	5 (9)	16:40	47 (16-85)	Case series
Imajo 2016 [38]	Japan	1	1 (100)	n/a	56	Case report
Kuan 2006 [39]	Taiwan	140	5 (4)	1:139	30 (20-52)	Case series
Shute 1984 [13]	Canada	269	36 (13)	NS	NS	Case series
Skinner 2007 [40]	Australia	7	1 (14)	1:6	13 (11-16)	Case series
Stirler 2016 [41]	Netherlands	30	1 (3)	10:20	45 (18-72)	Cohort retrospective
Towfigh 2013 [42]	United States	11	1 (9)	4:7	41 (15-64)	Retrospective case series
Total (n = 13)		613	62 (10)			

Data are presented as median [range], unless mentioned otherwise. N/A not applicable; NS not specified. [a] *Based on total study population.*

DISCUSSION

The anterior cutaneous nerve entrapment syndrome (ACNES) is a diagnostic struggle for various physicians ranging from surgeons, neurologists, gastroenterologists, pain specialists to general practitioners. As a result, ACNES is still often neglected as a possible cause of abdominal pain and discomfort and is considered a frequently overlooked diagnosis[3]. The diagnosis itself relies entirely on undertaking a thorough medical history combined with searching for sensitive clues at physical examination (circumscript pain localization, positive Pinch test, Carnett's test and abnormal sensory mapping). Conversely, imaging and laboratory evaluations are often noncontributing[7]. More complex subtypes of ACNES such as the bilateral variant likely are even harder to diagnose thus lengthening an already substantial diagnostic delay. The present study is the first to report on a large series of bilateral ACNES cases and aims to contribute to the awareness of this difficult variant. Moreover, the present data show that a bilateral variant is practically always (97%) observed in a symmetrical (mirrored) distribution. Conversely, only 3% of patients presented with an asymmetrical bilateral ACNES, i.e., a condition we consider as a coincidence of two concurrent unilateral cases.

Unilateral ACNES presents itself more frequently on the right side in a 4:1 ratio[7]. In more than half of the bilateral ACNES presentations (54% [75/138]), the onset was initially located at one side, either right or left, but also with a preponderance for right (60% *vs*. 40%). In a substantial portion of patients, however, pain shifted over time towards the contralateral side leading to identical sensory changes as observed at the starting side of symptoms. This peculiar phenomenon is known as mirror image sensory dysfunction (MISD)[13]. The phenomenon has been documented after surgery[14], nerve injury[15], in complex regional pain syndrome type[16] and in rheumatoid arthritis[17]. Following unilateral nerve injury, contralateral sensory dysfunction, defined as neuropathic pain characteristics such as allodynia and hyperalgesia, may occur in selected patients[18,19]. It has been suggested that these MISD-responses to an injury are qualitatively similar but smaller in magnitude and have a briefer time course compared to responses at the injury site[20]. However, tissue injury is not required to invoke MISD as observed in healthy individuals subjected to low-intensity stimuli[21]. Therefore, awareness of this phenomenon could aid physicians in understanding and recognizing future bilateral ACNES patients.

The origin of this bilateral distribution of pain and sensory dysfunction may either reside in the peripheral nervous system, the central nervous system or both. Several explanations may be forwarded. *First*, the medial branch of the anterior intercostal nerve may cross the midline, innervating the contralateral homologous paramedian skin area (Figure 9.4).

This would seem logical since a sharp demarcation border between different unilateral nerve innervation territories at least in the lower abdominal wall is absent[13]. Anatomical evidence for cutaneous nerves of the anterior abdominal wall crossing the midline has been presented[22]. An explanation of the bilateral projection of pain and the distribution of the sensory dysfunction thus may reside in the peripheral nervous system. *Secondly*, the observed bilateral symptoms

and sensory changes could be attributed to mirror-image sensory dysfunction (MISD).[22] Pursuing a physiological aspect, the nervous system exhibits a high degree of symmetry, which necessitates powerful transmedian communication systems to integrate and orchestrate the organism's homeostatic and behavioral mechanisms[20,23]. The exact underlying mechanisms of the transmedian communication, i.e., "cross-talk" in MISD is unclear but seems to rely on combined cellular and humoral events. A contralateral response might be induced by a glial cell inflammatory response with subsequent release of cytokines leading to activation of central neural nociceptive pathways[24]. However, one study showed a peripheral pathway where unilateral nerve injury led to production of tumor necrosis factor alfa (TNF-α) in the dorsal root ganglion (DRG) on the affected side[25]. It was hypothesized that TNF-α may diffuse via cerebrospinal fluid towards the contralateral DRG. TNF-α subsequently activates satellite glia to produce nerve growth factor (NGF) leading to long-lasting mechanical hypersensitivity leading to mirroring of pain[25]. While there is thus evidence supporting both mechanisms, further studying of this rare phenomenon is warranted to uncover transmedian signaling mechanisms as well to improve our understanding of how brain activity 'connects' both sides of the body.

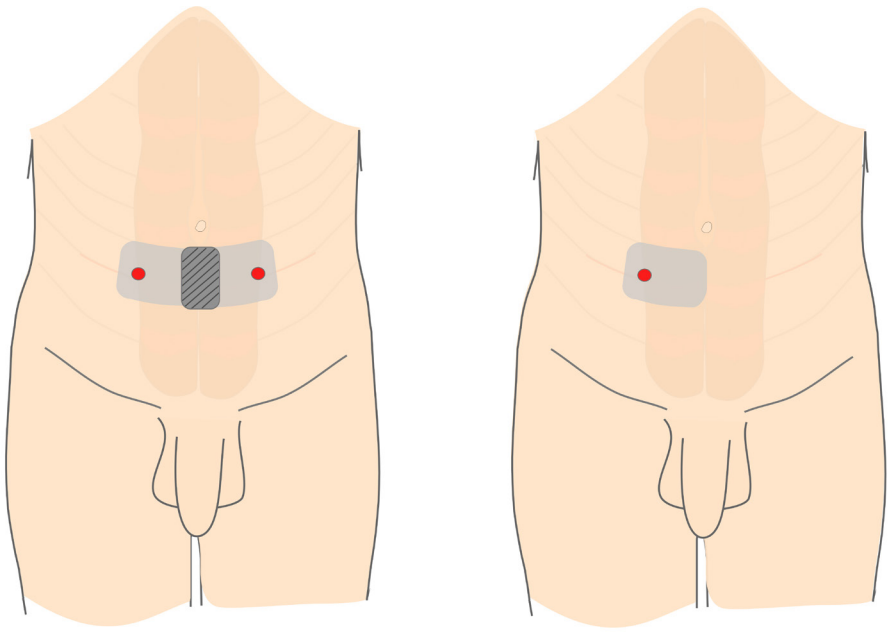

Figure 9.4:

Distribution of sensory disturbances in bilateral ACNES patients (left).

Light grey area on the right and left shows distribution of sensory disturbances that can be found by sensory mapping, with a point of maximal pain (red dot). The hatched grey area at the midline shows the most painful area experience by the patient with overlap of sensory disturbances from left to right, crossing the midline. On the right side distribution of sensory disturbances in unilateral ACNES patients is shown.

Neuropathic signs and symptoms may be suspected during extensive history taking using specific questionnaires suggesting neuropathic pain such as DN4, or following simple tests during physical examination[26,27]. In ACNES, a meticulous physical examination may reveal a circumscript pain localization, a positive Pinch test, a positive Carnett's test and/or sensory dysfunction such as hypo- or hyperesthesia or allodynia[7]. A remarkable observation was that a proportion of patients reported that the experienced pain was most intense in the midline, presenting with corresponding sensory disturbances on both sides. This is practically always accompanied by other ACNES characteristics such as a positive Carnett's test and the Pinch test being symmetrically present on both sides of the abdomen. The above highlighted anatomy with midline crossing nerves may explain why the maximum pain is often felt in the very midline. We have also evaluated a number of patients with such a symmetrical bilateral pain syndrome at the umbilical level (T10) who were referred following an unsuccessful umbilical hernia repair elsewhere. Moreover, it may very well be that an initial neglect for the contralateral side could lead to this specific type of pain being overlooked, as is observed in ACNES in general[3]. Therefore, a physician should be aware of these bilateral presentations by frequently repeating ACNES-tests on the contralateral side[7].

Apart from a more complex diagnostic pathway, an adequate treatment plan for bilateral ACNES is possibly even more challenging. Studies in type I complex regional pain syndrome (CRPS), demonstrated that recurrences in patients with bilateral presentations occur more frequently[16]. In this series of 1116 ACNES patients, 98 of 142 (69%) bilateral ACNES cases proceeded to undergo a neurectomy. In the unilateral group (n=970), this number was 591/970 (61%). This difference is possibly due to the fact that unilateral patients respond slightly better to conservative treatment measures compared to bilateral ACNES cases. Our results also found a lower total success rate after bilateral anterior neurectomy (approximately 50%) compared to existing numbers on unilateral ACNES (70%)[7]. Some patients reported that surgical intervention cured one side adequately, but did not lead to a successful result on the contralateral side. However, these seemingly inferior success rates have to be judged in the right context. When assuming that bilateral ACNES in fact are two independent ACNES entities, the a priori success rate after bilateral neurectomy is as low as 50%, as this can be estimated to be $(0.7 * 0.7) * 100 \approx 50\%$. This theoretical number correlates well with the observed success rate in the present study (some 54%). These considerations are important in counseling a patient prior to operation. Nevertheless, our experience is that bilateral ACNES is associated with lower complete success rates regularly requiring additional interventions.

We are aware of the limitations of the present study. An important limitation is the neglect of studying potential abnormalities in central pain processing in this subpopulation. Quantitative Sensory Testing (QST) is a validated and commonly used tool for evaluating central nociceptive processing[28]. Treatment modalities that are directed at the nociceptive source (i.e. the pain generator) can be expected to be less efficacious in the presence of central sensitization[29]. Since no QST tests were used in this large cohort, this effect remains unclear.

Lastly, the diagnosis of ACNES in this cohort was neither established by objective tests such as laser evoked potentials, or nerve biopsies, nor by specific questionnaires suggesting neuropathic pain, including DN4, LANSS or PainDETECT[26,27]. However, we hypothesize that the presently used tests during physical examination have sufficient diagnostic sensitivity.

In conclusion, this is the first large study reporting on the characteristics of patients with a bilateral ACNES. It is thought that this variant represents an example of mirror image sensory dysfunction (MISD). This study adds to the existing knowledge helping physicians to adequately recognize and treat this complex subpopulation of ACNES patients. Further fundamental research is needed to fully understand its complex underlying mechanisms.

Conflicts of interest and source of funding

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CHAPTER 10

Summary, conclusions and general discussion

SUMMARY

Chronic abdominal pain (CAP) is usually attributed to the presence of a diseased internal organ[1]. Identifying the cause of CAP often requires multiple investigations such as laboratory testing, ultrasound imaging or CT-scans in the search for a visceral cause. However, up to 30% of CAP patients suffer from pain that originates from the abdominal wall rather than from a viscus[2]. CAP in these individuals may be due to anterior cutaneous nerve entrapment syndrome (ACNES) although this diagnosis is frequently not considered[3]. ACNES is thought due to the entrapment of end branches of intercostal nerves T7-12. Failing to acknowledge the abdominal wall as potential origin of CAP often results in erroneous diagnoses and consequently ineffective treatment modalities. It is obvious that these diagnostic struggles result in a high consumption of medical resources and high healthcare expenditure[3,4].

There is ample evidence to support the contention that ACNES is often overlooked as a cause of severe CAP. A clear set of diagnostic criteria would aid in diminishing this neglect. Recent studies attempted to develop adequate diagnostic tools for the identification of ACNES. A questionnaire was found to accurately distinguish irritable bowel syndrome (IBS) or functional abdominal complaints from an abdominal wall related pain such as ACNES[5]. Furthermore, 2 randomized clinical trials on therapeutic abdominal wall injections and a surgical neurectomy procedure (removing end branches of intercostal nerves T7-12) in a placebo-controlled fashion offered high level scientific evidence demonstrating the existence of this entity. Accumulating sound scientific research has contributed to an increased awareness of ACNES and may potentially lower incorrect diagnosis rates in patients suffering from CAP.

Most evidence on the existence of ACNES was initially based on case series of limited volume. Due to our large experience as a Dutch tertiary referral center for CAP, we were in the position to evaluate increasing numbers of patients with ACNES over the years. This unique opportunity has led to a large database including >1100 patients whose characteristics and specifics of physical examination are presented in **chapter 2.** Since objective measures determining if a patient has indeed ACNES are hitherto absent, the diagnosis is currently established by history taking and a meticulous physical examination. Studying the largest patient series to date has indicated that the diagnosis ACNES was highly likely if a patient with a localized chronic abdominal pain had at least two out of four characteristics: localized sensory disturbances covering the area of maximal abdominal pain (either hypoesthesia, hyperalgesia, altered cold perception), a positive Pinch sign, a positive Carnett sign, and a positive response (>50% pain reduction) to a rectus sheath block. These 4 characteristics were present in the majority of these more than 1100 patients (78%, 78%, 87%, and 81%, respectively). Our series also showed that an anterior neurectomy was associated with a 72% short term success rate, a percentage that is quite comparable to results earlier reported in literature[6,7].

Pulsed radiofrequency (PRF) for ACNES

While conservative therapies such as abdominal wall injections as well as invasive techniques including neurectomy have been extensively studied in recent literature, little is known regarding minimal invasive treatment strategies for ACNES. Two case reports recently described the use of PRF in ACNES patients, highlighting its treatment potential[8,9]. PRF applies an electromagnetic field around the potentially affected nerve using an electrical current led through a special cannula. As a result, neuronal membranes are changed and thereby interfere with the firing rate of action potentials[10]. The anaesthetic effect of PRF is caused by this alteration in synaptic transmission. However, both case reports described the use of PRF at the level of the dorsal root ganglion (DRG), whereas evidence of a potential efficacy at the level of the anterior abdominal wall is unknown. **Chapter 3** has filled this knowledge gap and describes, retrospectively, 26 ACNES patients receiving PRF treatment at anterior portions of the abdominal wall. Short term treatment success, defined as >50% pain reduction after 6-8 weeks, was attained in half of the study population, whereas 4 patients were pain-free on the long term (median follow up 15 months, range 3-26). The observed median effect duration was 4 months (range 3-26) and is in line with research on PRF in other pain syndromes[11,12].

Stimulated by these promising results, a RCT was designed to compare the efficacy of PRF with anterior neurectomy on pain relief in ACNES patients responding well (but temporary) to abdominal wall infiltrations using a local anesthetic agent (**chapter 4)**. Sixty-six patients were randomized to either PRF or anterior neurectomy, in a non-blinded, crossover fashion. The primary outcome was the number of patients reaching >50% pain reduction using a NRS scale at 8 weeks of follow-up. Secondary outcomes included patient satisfaction, quality of life, use of analgesics and adverse events. Whenever PRF patients were not satisfied with the treatment result at 8 weeks follow-up, a cross-over to neurectomy was optional.

In **chapter 5,** the results of this trial are presented. Success was attained in 61% (17/28) of the neurectomy patients vs 38% (12/32) in the PRF group (P>0.05). Neurectomy participants experienced a greater percent change in NRS pain scores from baseline (-47.7, 95% confidence interval [CI] -64.8 to -30.6), than participants in the PRF group (-24.7, 95% CI -41.6 to -7.9; P = 0.056). Thirteen PRF patients decided not to undergo their scheduled surgery as pain relief was considered sufficient. Secondary outcomes and adverse events rates were comparable between groups. It was concluded that PRF is a safe and effective treatment option in some patients refractory to conservative pain treatment strategies. As a consequence, PRF may be considered in ACNES before proceeding to surgical interventions.

Subtypes of ACNES

ACNES is possibly caused by the entrapment of *anterior cutaneous* branches of the thoracic spinal nerve at the lateral borders of the rectus abdominis muscle. This thoracic spinal nerve is usually anchored at three sites: (1) at the back where the posterior branches of the thoracic nerve originate, (2) at the flank where the lateral branch originates and (3) at the anterior abdominal wall where the nerve enters the rectus abdominis muscle[13]. A previously mechanical theory suggested that a too tight anchor may cause ischemia and severe pain at any of these three locations [1]. Although most patients who are referred to Solvimáx are suffering from either ACNES or groin pain, small subpopulations presented with different symptoms. These subgroups were in fact having a pain pattern that were rather different from a straight forward ACNES. In **chapter 6,** a 26-year old female was found to have chronic back pain due to a local entrapment of posterior branches of the thoracic spinal nerve (POCNES). A neurectomy procedure cured her debilitating pain. After 2 years of follow-up, she was still experiencing pain relief. This condition was not previously reported in the literature. **Chapter 7** reports a case series of 14 patients who were diagnosed with this new pain syndrome termed POCNES. They were treated with local injections of lidocaine and, if pain was refractory, a neurectomy procedure. Seven out of 11 patients benefitted from surgery. A 57% long-term efficacy rate was obtained using this treatment algorithm (median 29 months follow-up, range 5-48).

Another novel subtype of ACNES was found in patients with localized chronic flank pain as characterized by sensory abnormalities of the flank skin, a positive Pinch and a positive Carnett test. This new syndrome was coined Lateral Cutaneous Nerve Entrapment Syndrome (LACNES). **Chapter 8** elaborates on the specifics of this peculiar pain syndrome and proposes a diagnostic and treatment protocol. Study results of 30 patients diagnosed with LACNES demonstrated that over half was successfully treated with local tender point infiltrations using lidocaine 1% (median 40 months follow-up, range 2-103).

Most ACNES patients present with a unilateral abdominal wall pain. One remarkable finding in our large series of ACNES patients (**chapter 1**) was that 1 in 8 ACNES patients was found to have a bilateral variant. It was hypothesized that a complex underlying mechanism of 'communicating' neural pathways may occasionally result in bilateral pain. Mirror image sensory dysfunction (MISD) may occur in the presence of a one-sided peripheral nerve lesion leading to a similar development of pain on the contralateral side of the body ('mirrored')[14]. Contralateral sensory dysfunction, defined as neuropathic pain characteristics such as allodynia and hyperalgesia, may occur in these selected patients[15,16]. In **chapter 9**, specifics of 146 bilateral ACNES patients and treatment results are presented. Patient characteristics and findings on physical examination were essentially not different from unilateral cases of ACNES although overall treatment success was slightly lower. A literature search demonstrated that 10% of all ACNES cases are bilateral, a percentage that is comparable to rates observed in our center, which was some 13%. We concluded that bilateral ACNES is a complex variant of ACNES but the exact underlying pathological mechanism, as in unilateral ACNES, is unclear.

CONCLUSIONS

1. An ACNES patient is typically a young or middle-aged female with a localized anterior abdominal pain. The diagnosis may be considered in the presence of sensory disturbances at the area of maximal pain, a positive Pinch sign, a positive Carnett sign or a positive response (> 50% pain relief) to abdominal wall infiltration using an anesthetic agent.
2. Pulsed radiofrequency (PRF) is a minimally invasive, safe and feasible treatment option in ACNES patients.
3. PRF could reduce the need for a neurectomy procedure and should therefore be considered if conservative measures fail.
4. In patients with chronic flank or back pain, a careful history taking and physical examination using simple somatosensory testing (cotton swab, pinch test) may reveal a neuropathic pain syndrome such as LACNES or POCNES.
5. Injection therapy is long term effective in over half of LACNES patients.
6. A surgical neurectomy for POCNES leads to a 64% success rate.
7. A bilateral pain syndrome may be present in 1 of every 8 patients with ACNES. It has similar patient characteristics and findings on physical examination, but complete treatment success is lower.
8. The exact underlying mechanisms in mirror image pain pathogenesis leading to bilateral ACNES are yet to be defined.

DISCUSSION

Neuropathic pain and ACNES

The International Association for the Study of Pain (IASP) defines neuropathic pain as 'pain caused by a (demonstrable) lesion or disease of the somatosensory nervous system'[16]. ACNES is a chronic abdominal wall pain syndrome (CAP) that is categorized as a neuropathic pain syndrome. The pathogenesis of ACNES is currently based on the entrapment theory as proposed by Applegate in the 1970's[13,17]. The thoracoabdominal nerves provide anterior, lateral and posterior branches to supply skin sensations of the trunk. Peripheral nerve entrapment usually occurs at specific anatomic sites where the nerve is forced to alter its direction by entering a fibrous or osseofibrous tunnel, or where local pressure on the nerve leads to mechanically induced irritation[18]. As a consequence, localized swelling is thought to injure the nerve directly or affecting the nerve's circulation. This chain of events leads to ischemia and pain and a vicious circle[1,19]. In ACNES, there may not always be a distinct 'lesion' of the concerning nerve at hand challenging the IASP's definition of neuropathic pain. However, recent abdominal surgery is a major cause of ACNES as direct or indirect abdominal wall tissue injury can lead to neuropathic pain (**chapter 2**).

While IASP's definition of neuropathic pain has recently been updated, discussion still exits whether one may or may not call a pain syndrome 'neuropathic'. A distinct lesion of the nerve leading to neuropathic pain is established by investigations such as objective tests including laser evoked potentials, nerve biopsies, Quantitative Sensory Testing, or MRI imaging[16,20]. Furthermore, specific questionnaires suggesting neuropathic pain, such as the Douleur Neuropathique (DN-4), the Leeds Assessment of Neuropathic Symptoms and Signs. (LANSS), Pain DETECT, or the Neuropathic Pain Syndrome Inventory (NPSI) could be used to strengthen the observation of a neuropathic rather than a nociceptive pain syndrome[20]. However, some diseases are considered neuropathic pain disorders based only on their clinical presentation (such as trigeminal neuralgia), although objective tests are lacking. The same situation may be at hand in ACNES. Our patients also typically experience tingling, burning and/or electrical-like sensations and pain resulting from non-painful stimulations (such as light touching). They also typically have somatosensory disturbances in a specific peripheral small area. Moreover, the symptoms also persist and have a tendency to become chronic and respond less to pain medications. However, in **chapter 5 and 7,** a 7-point version of the DN4 with a ≥3 cut-off point suggestive of neuropathic pain was used to discriminate between neuropathic and non-neuropathic pain in ACNES[21,22]. As expected, using this DN-4 in ACNES patients resulted in a median score of 3 indicating the neuropathic character of the syndrome.

Central sensitization in ACNES

A consistent finding throughout this thesis is the long diagnostic delay in patients who are ultimately diagnosed with ACNES, LACNES or POCNES. Peripheral and central neuropathic pain are both associated with sensory skin abnormalities. Central sensitization may also manifest itself as hypersensitivity such as allodynia or pressure hyperalgesia[23]. Central pain is thought to result from ongoing nociceptor inputs triggering a prolonged increase in excitability and synaptic efficacy of neurons in central nociceptive pathways[23]. In ACNES patients, central sensitization may possibly occur due to elevated pressure in the rectus muscle compartment, leading to ischemia and chronic edema of the nerve's perineurium and endoneurium leading to dysfunctional firing of the nerve[24]. Subsequently, pain sensations become totally independent of a peripheral drive[25,26]. One may assume that a local treatment directed at the peripheral nociceptive source is destined to fail in the presence of central sensitization[27].

A study by Rijckevorsel et al., assessed pain processing in ACNES patients who were either refractory or responsive to treatment using Quantitative Sensory Testing[28]. Unsuccessfully treated ACNES patients exhibited more signs of sensitized segmental and central pain processing as reflected by lower pressure pain thresholds compared to responsive or successfully treated ACNES patients. They also found that doctor's delay and treatment failure were interrelated. In contrast, a recent report of Mol et al. studying predictive factors associated with poor outcome in ACNES patients did not identify doctor's delay as a negative parameter[29]. Furthermore, the observations by Rijckevorsel et al. are possibly selection biased as pre-intervention QST were not performed. In these unsuccessful patients possibly suffering from central pain, medication targeting central pain processing such as gabapentinoids or tricyclic antidepressants may be explored[30].

Segmental relations and ACNES

It must be appreciated that ACNES is a diagnosis per exclusionem. One of the major criteria supporting the diagnosis is the absence of visceral disease as demonstrated by laboratory tests or imaging[6]. However, this assumption may be too simplistic. **Chapter 7** highlights the existence of so called 'segmental relations' between viscera and the abdominal wall in LACNES patients. The concept of a segmental relation is not new and was described by Sir Henry Head more than a century ago[31]. He explained that the presence of visceral disease may be associated with cutaneous manifestations such as hyperalgesia or allodynia. Connections between visceral afferent nerve fibers and somatic cutaneous pain afferents at the level of the dorsal root ganglion may explain these somatosensory phenomena. The mechanism of segmental associations was also described in patients having acute appendicitis[32]. It was found that a large portion of these patients also had altered right lower abdominal wall skin sensations just prior to the appendectomy. However, these phenomena were transient as cutaneous skin sensation normalized in the postoperative weeks in the vast majority of these patients. Therefore, differentiating between neuropathic pain and visceral pain is complex. On the other

hand, the presence of altered somatosensory skin sensations can direct a clinician towards the presence of an underlying visceral cause. Our experience in LACNES patients suggests that a visceral source of the pain must always be excluded, and treated if present, also because curing the visceral disease led to disappearance of neuropathic pain symptoms in a portion of our LACNES patients.

Differential diagnosis of ACNES-like entities

While diagnosing the somewhat mysterious ACNES syndrome is rather difficult, determining LACNES or POCNES is an outright challenge. The differential diagnosis of these pain syndromes is diverse including a number of visceral diseases as well as 'spine related' pain or post-surgical pain syndromes. Therefore, a thorough physical examination is needed since serious underlying pathology could be the cause of the symptoms. Moreover, imaging including ultrasound, CT-scans or MRI of soft tissue as well as bone is essential.

Chapter 8 reported on LACNES due to nerve entrapment as a cause of chronic flank pain. One may question whether there is a high overlap in symptoms between LACNES and several other diagnoses. It is thought that all three syndromes (ACNES, LACNES and POCNES) represent some form or subtype of an intercostal neuralgia (ICN). ICN is defined as a neuropathic pain disorder due to compression or injury of the intercostal nerves[33]. In essence, a variety of pain sensations can be experienced including a burning, sharp, aching, or even dull pain. This pain is usually present along the whole tract of the intercostal nerve and its accompanying dermatome. A major difference with LACNES is the finding that pain in ICN spreads more diffusively rather than a specific small fingertip tender point as we observed in LACNES. Another syndrome with a somewhat similar presentation as LACNES is the rib-tip syndrome[34,35]. In this entity, unilateral (or bilateral) pain is provoked by a static load such as prolonged sitting and standing, trunk rotation and/or walking. As a result, the distal end of the 11th or 12th rib touches the iliac crest. A deteriorating thoracolumbar scoliosis or osteoporosis is usually the cause of a rib-tip syndrome. However, it can be distinguished from LACNES using physical examination as pain in patients with rib-tip could be provoked by extensive lateroflexion since the space between the 11th or 12th rib and the iliac crest is then reduced. Moreover, somatosensory disturbances in these patients are often absent.

While a secure history taking and physical examination could help to differentiate between LACNES and several other diagnoses, the same accounts for patients presenting with chronic lower back pain. This entity may be due to mechanical dysfunctioning, a neuropathic disorder, or secondary to other conditions[36-40]. As reported in **chapter 6 and 7**, POCNES was established as a potential cause of chronic back pain. Several other syndromes mimic signs and symptoms as observed in POCNES, such as thoracic radicular pain, thoracic facet pain and the thoracolumbar syndrome (TLS, also known as Maigne's syndrome)[38,39,41]. Differentiating between these conditions is challenging.

In conclusion, the role of a thorough physical examination is crucial in recognizing LACNES or POCNES as symptoms of several conditions causing flank and/or back pain are frequently overlapping. Somatosensory testing using swab and alcohol gauze may demonstrate the presence of skin hypo- and dysesthesia and altered cool perception in the area covering the painful spot. Localizing a small area of maximal pain within this area of altered skin sensation could point towards the presence of a local nerve entrapment as seen in ACNES, LACNES and POCNES.

Pulsed Radiofrequency in ACNES

Research on alternative treatment forms of ACNES that are less invasive than surgery is rather scarce. Although lacking a scientific foundation, PRF is utilized in several other pain syndromes[42-44]. **Chapter 3 and 5** present retrospective and prospective data supporting the efficacy of PRF in ACNES. To our knowledge, these two studies are the first large studies worldwide on the efficacy of PRF in ACNES. In our randomized controlled trial, 4 of 10 patients reported success at the short-term. Moreover, 13 patients (40%) withdrew from a scheduled neurectomy. Although this type of surgery is associated with very few complications, PRF could lead to fewer surgical interventions in a random ACNES population and thereby costs are likely reduced as general anaesthesia and hospitalization are avoided.

Although these first reports are promising, it remains to be seen whether PRF is long term effective. There are no studies to date that evaluate long-term follow up (≥12 months) of PRF in ACNES patients. Furthermore, the optimal parameters for application of PRF have yet to be determined[45]. Cosman and Cosman stated as early as 2005 that unlike continuous radiofrequency, achieving optimal parameters for a desired clinical objective using PRF will need more experience and a better understanding of the electrical and thermal field effects on neurons[10]. It is therefore hypothesized that optimizing the parameters of a PRF procedure will likely influence treatment results. While this thesis opens doors to a new treatment option in ACNES, the currently proposed treatment algorithm including PRF is still far from excellent.

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CHAPTER 11

Future perspectives

FUTURE PERSPECTIVES ON ACNES

The clinical entity of ACNES is now well increasingly recognized due to cumulating evidence provided by various centers all over the world gaining experience in diagnosing and treating these patients. Both diagnosis and treatment options were recently studied in well-designed randomized controlled trials[1-3]. It is imperative to initiate studies determining beforehand whether patients respond favorably to surgery prior to initiating invasive therapy. A recent study by Mol et al, identified pain medication use, presence of paravertebral tender points, previous abdominal surgery and failure to respond to a diagnostic rectus block as factors predicting success[4]. However, it is obvious that these patient characteristics are not the only factors influencing treatment success.

For instance, pain catastrophizing is conceptualized as a negative cognitive–affective response to anticipated or actual pain and has been associated with a number of important pain-related outcomes. The pain catastrophizing scale (PCS) was developed to study the mechanisms by which catastrophizing has an impact on pain experience[5]. Several studies suggested that presurgery catastrophizing indeed predicts postsurgical pain[6,7]. The hospital anxiety depression scale (HADS) was also developed to assess states of depression and anxiety influencing effects of surgery[8,9]. Both catastrophizing as well as depression likely influence treatment outcome in ACNES patients. However, these questionnaires were not explored in ACNES patients yet. Implementation of these scores in future research could aid in determining whether psychological predisposition has an influence on treatment success. Consequently, these analyses could allow for optimizing patient counselling and selection.

The exact etiology of ACNES still remains unknown. Previous studies showed that the majority of patients had a 'spontaneous' start of their symptoms and could not remember a clear triggering event. It is hypothesized that the pathophysiology of ACNES is more complex than previously thought. For instance, the potential correlation with a previous varicella zoster infection requires additional investigations. A differential approach regarding the vaccination of varicella is present in most European countries[10,11]. Population studies among these countries may identify a possible relationship with ACNES. Furthermore, there is a condition of dermatomal pain in the absence of an antecedent rash termed 'Zoster Sine Herpete' (ZSH)[12]. Reactivation of the varicella zoster virus (VZV) could lead to this condition in some cases. It is also associated with multiple neurologic complications, including meningoencephalitis, myelitis, ocular disease and post herpetic neuralgia (PHN)[13]. The clinical picture includes symptoms associated with ACNES so pathological mechanisms should be explored.

While ACNES is a clinical diagnosis that is established by a profound history taking and physical examination, some other diagnostic tools are not evaluated in ACNES patients yet. No 'imaging' techniques are known to objectively identify painful areas in ACNES patients. Since the distribution of body heat in a normal body is symmetrical, some hypothesized that thermography could be used as an imaging tool of neuropathic pain[14,15]. Furthermore, since

pain is a predominant subjective perception, quantitative sensory testing (QST) may possibly be used to assess alterations in nociceptive and pain processing at peripheral and central levels of the nervous system in ACNES. It would be interesting to ascertain whether differences to QST testing do exist in ACNES patients, and if so, if they are predictive of a successful treatment[16]. An explorative study was published but additional research is needed before founded conclusions can be drawn[17].

The present thesis also focuses on a new minimal invasive treatment option for ACNES patients termed Pulsed Radiofrequency (PRF). While PRF has been studied in several other pain syndromes, important information regarding the exact working mechanisms remain unknown. Although used in clinical practice for more than two decades, the optimal parameters for application of PRF have yet to be determined[18]. Well-designed future studies should further look into specifics of PRF treatment including optimal cannula position, stimulation thresholds as well as PRF generator parameters[19]. While PRF in the present thesis was examined at the level of the abdominal wall, evaluation of PRF application at the level of the dorsal root ganglion (DRG) may also be worthwhile[20,21].

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CHAPTER 12

Valorisation

INTRODUCTION

Chronic abdominal pain (CAP) is defined as intermittent or constant abdominal pain that has been present for at least two months[1]. CAP may be due to an abdominal *wall* related origin. Several studies have demonstrated that up to 30% of patients with CAP of an unknown source in fact suffer from an abnormality in the abdominal wall[2-4]. Anterior Cutaneous Nerve Entrapment Syndrome (ACNES) is caused by entrapment of end branches of intercostal nerves that are residing in the abdominal wall. Exact numbers on incidence of ACNES patients are unknown. However, the incidence in patients evaluated for acute abdominal pain in an emergency department of a large teaching hospital was estimated at approximately 2%[5]. Considering the fact that a substantial number of physicians are not aware of the ACNES syndrome yet, actual numbers of patients suffering are likely higher.

Several aspects of this pain syndrome were unveiled during the last two decades but a tremendous lot of work still needs to be done. An important goal is to increase awareness among physicians, and not only regarding entrapment syndromes that are situated at *ventral* portions of the trunk. The present thesis also highlighted variants of ACNES causing a chronic type of flank or back pain. These entities were hitherto not recognized. Since experiencing a persistent undiagnosed pain is most frustrating, one can imagine the vast consequences of spreading this knowledge. The same accounts for exploring new treatment forms (such as Pulsed Radiofrequency, PRF) in order to cure a larger portion of patients in a minimally invasive manner. It is to be hoped that other research groups will also pursue these important aspects of ACNES and initiate validation studies.

SOCIAL RELEVANCE

Chronic pain has been a mystery for centuries. Descartes once tried to explore the pathophysiology of chronic pain in his "Treatise of Man" and compared mankind with a machine with intricate and fine-tuned systems within systems[6]. He also described a hollow pathway controlling sensory and motor perception as well as a pain pathway. Since then, pain remained a complex entity in the field of medicine, and more and more research has accumulated over the years. However, several features such as determinants, pathogenesis, prevention, treatment and prognosis of pain are still largely unknown. In the present thesis we encountered two remarkable features of pain. **Chapter 8** suggested that, in some presentations of neuropathic pain, a segmental relation between a visceral abnormality and the abdominal wall may possibly explain somatosensory abnormalities. The pathway of visceral afferent nerve fibers converging with cutaneous pain afferents at the level of the dorsal root ganglion and spinal cord possibly explains why neuropathic pain symptoms may manifest itself once visceral disease occurs[7-9]. It is advised to always exclude a visceral cause of a neuropathic abdominal, flank or back pain using imaging.

Furthermore, **chapter 9** illustrates that ACNES may present itself in a bilateral fashion. It was hypothesized that a one-sided peripheral nerve lesion can lead to a similar distribution of pain on the contralateral side of the body in a 'mirrored fashion'. This concept which is known as mirror image sensory dysfunction (MISD) is a complex pain mechanism that is also present in several other pain syndromes including complex regional pain syndrome[10]. While these two mechanisms may just play a small role of the pathogenesis of pain in general, recognizing and understanding these concepts is a valuable asset as diagnosis and treatment may be improved.

From a socio-economic point of view it must be appreciated that pain with neuropathic characteristics is generally severe and associated with a poor overall health status[11]. Moreover, difficulty in diagnosing ACNES could lead to excessive blood testing and imaging studies causing a psychological, physical and economic burden to patients[12]. While ACNES is one of the many pain conditions that received much attention in the last two decades, **chapter 2** provides an overview of specific characteristics based on a cohort of 1116 patients, and thereby provides diagnostic criteria. It is hoped that these criteria reduce the medical costs of these chronic pain patients since physicians may possibly recognize the syndrome earlier, or even at 'at first sight'.

SOCIETAL IMPACT

Over the years, research on ACNES was not only published in scientific journals but was also presented on several national and international meetings of different specialties. Furthermore, our institution launched a website containing valuable information for both the patient and the doctor (www.buikpijn.nl). Moreover, the first Dutch ACNES patient society was recently (2018) founded. During the modern-day era it is extremely important to educate (young) patients who are more and more focused on online sources of information rather than on the doctor himself. In addition, if current treatment modalities fail, people will find solidarity in peers also suffering from chronic pain.

Patients with ACNES usually present after a long doctor's delay as was shown in the present thesis. To reduce delays, and diminish the emotional burden of patients suffering from chronic pain, as well as making information available for the public, an initiative of creating a nation-wide ACNES network was started in 2018. It consists of hospital specialists from 32 Dutch hospitals who joined forces to conceive a platform. Potential patients can thus be referred to a proper regional hospital that is skilled in the management of ACNES.

RELEVANCE IN THE MEDICAL FIELD

An ongoing debate within pain medicine is clinical relevance of outcome measures[13,14]. Most studies focus on pain relief using a range of different pain scales. However, patients respond differently to therapies, and the question is what 50% pain reduction means when in some patients 100% pain remission is achieved. As observed in several studies in the present thesis, some patients tend to be overall satisfied with their treatment outcome although pain has not completely disappeared, and in some cases not even reached the 50% pain reduction level. Therefore, pain relief is not always reflecting patient satisfaction. This apparent contradiction is due to the fact that satisfaction is a multi-factorial measure of outcome. Not only does it depend on pain relief but it is also subject to patient expectations and experienced burden of complaints (quality of life). In our randomized controlled trial (**chapter 5)**, we used pain scores as well as satisfaction as outcome measures. We recommend to standardly include patient satisfaction as an important outcome parameter in the evaluation of any new treatment form.

The present thesis highlighted new information regarding diagnosing and treating ACNES-like entities causing chronic flank or back pain. A similar treatment protocol as used in ACNES, e.g. local infiltrations using lidocaine, followed by surgical neurectomy whenever symptoms were persistent, was proposed in LACNES and POCNES. Local injections using lidocaine were long-term effective in more than half of the LACNES patients. Furthermore, a surgical neurectomy in POCNES achieved a 64% success rate. An interesting study of the present thesis focussed on the use of PRF as a minimally invasive treatment option. PRF is an example of such a new treatment that is increasingly used for a variety of conditions but sometimes with rather limited scientific evidence[15,16]. Our RCT showed that 4 of 10 patients achieved success after 8 weeks, and that in 13 of 32 patients a surgical intervention was aborted. These findings demonstrate the potential of PRF as a viable treatment option in ACNES, reducing the need for surgery and thereby limiting direct and indirect costs of the overall treatment. Patients are satisfied with PRF treatment and even esthetically it is beneficial since no scar is created. Therefore, PRF is considered a reliable and safe first choice treatment option in ACNES patients who fail conservative treatment measures. It is advised to incorporate PRF as an potential viable step in a future optimal, tailor made treatment algorithm in ACNES.

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CHAPTER 13

Samenvatting (Dutch summary)

DUTCH SUMMARY (SAMENVATTING)

ACNES

Chronische abdominale pijn (CAP) wordt vaak veroorzaakt door een orgaan gerelateerd probleem[1]. Het identificeren van de onderliggende oorzaak van CAP leidt vaak tot veel onnodige en kostbare diagnostische onderzoeken, waaronder bloedanalyses, echografie en CT-scans. In ongeveer 30% van de gevallen heeft de pijn geen viscerale oorzaak, maar is de buikwand de boosdoener[2]. CAP wordt bij deze patiënten soms door het anterior cutaneous nerve entrapment syndrome (ACNES) veroorzaakt, hoewel er vaak niet aan deze diagnose wordt gedacht[3]. ACNES ontstaat door beknelling van eindtakken van de laatste 6 thoracale intercostale zenuwen (Th7-12). Het niet onderkennen van deze entiteit als oorzaak van CAP kan leiden tot foutieve diagnoses en overbodige en zinloze behandelingen. Een diagnostische zoektocht kan soms leiden tot een groot verbruik van medische hulpmiddelen en hoge zorgkosten[3,4].

Er is momenteel voldoende wetenschappelijk bewijs voorhanden waaruit blijkt dat ACNES vaak over het hoofd wordt gezien als oorzaak van ernstige CAP. Duidelijke diagnostische criteria zouden kunnen bijdragen aan de herkenning van dit buikwandpijnsyndroom. Recente studies hebben geprobeerd diagnostische 'handvatten' te ontwikkelen voor het vaststellen van ACNES. Er is een specifieke vragenlijst ontwikkeld die onderscheid poogt te maken tussen het prikkelbare darmsyndroom of functionele buikklachten enerzijds, en een buikwandpijnsyndroom zoals ACNES anderzijds[5]. Daarnaast leverden twee gerandomiseerde placebo-gecontroleerde studies, gericht op therapeutische buikwandinjecties en een neurectomie (verwijdering van de zenuwuiteinden van intercostaalzenuwen Th7-12), sterk wetenschappelijk bewijs voor het bestaan van deze entiteit. Deze groeiende stapel van kwalitatief sterk onderzoek zorgt voor meer onderkenning van ACNES en leidt mogelijk tot minder incorrecte diagnoses bij patiënten die lijden aan CAP.

Eerder wetenschappelijk bewijs voor het bestaan van ACNES bestond hoofdzakelijk uit relatief kleine patiëntenseries. Door onze rol als tertiair verwijscentrum voor CAP was het mogelijk een groeiend aantal ACNES patiënten over de jaren heen te evalueren. Dankzij deze aanwas kon een grote database worden opgezet met >1100 patiënten, van wie karakteristieken en details van lichamelijk onderzoek worden weergegeven in **hoofdstuk 2**. Er zijn helaas geen duidelijke objectieve meetinstrumenten om vast te stellen of er daadwerkelijk sprake is van ACNES. De diagnose wordt daarom gesteld op basis van anamnese en een nauwgezet lichamelijk onderzoek. Door de informatie uit deze database te analyseren kon worden geconcludeerd dat de diagnose ACNES aannemelijk is als een patiënt met een plaatselijke chronische buikpijn aan minstens twee van de volgende karakteristieken voldoet: lokale sensibiliteitsstoornissen (hypesthesie, hyperalgesie of veranderde koude perceptie) in het huidgebied rondom het maximale pijnpunt, een positieve Pinch-test, een positieve test van Carnett en een positieve response (> 50% pijnreductie) op een lokale rectusschede blokkade. Deze vier karakteristieken bleken aanwezig bij de meerderheid van deze >1100 patiënten (respectievelijk 78%, 78%, 87%

en 81%). Ditzelfde onderzoek laat zien dat een anterieure neurectomie op korte termijn een succespercentage van 72% heeft, een percentage dat vergelijkbaar is met de resultaten uit eerdere retrospectieve en prospectieve studies[6,7].

Pulsed radiofrequency (PRF) bij ACNES

In de recente literatuur zijn zowel conservatieve behandelopties (buikwandinjecties) als invasieve therapieën (neurectomie) uitgebreid bestudeerd, terwijl er eigenlijk nog maar weinig bekend is over andere minimaal invasieve behandelopties voor ACNES. Recent zijn twee casussen beschreven waarbij Pulsed Radiofrequency (PRF) is toegepast bij ACNES patiënten[8,9]. Bij PRF wordt echogeleid via een speciale canule een elektromagnetisch veld rondom de aangedane zenuwtak aangebracht. Dit veld zorgt voor een verandering in het neurale membraan, hetgeen vervolgens interfereert met de normale frequentie van actiepotentialen[10]. Het analgetische effect van PRF lijkt te worden veroorzaakt door deze verandering in synaptische transmissie. In eerdergenoemde twee case reports wordt het gebruik van PRF ter plaatse van het dorsale hoorn ganglion (DRG) beschreven. Wetenschappelijk bewijs voor het potentiële effect van PRF op rectus niveau ontbrak echter tot op heden. Dit kennishiaat wordt opgevuld door **hoofdstuk 3**, waarin 26 ACNES patiënten die behandeld zijn met PRF op het voorste rectusniveau, retrospectief worden beschreven. De helft had na 6-8 weken >50% pijnreductie en was dus succesvol behandeld. Van deze 13 patiënten bleven er 4 ook op lange termijn pijnvrij (mediane follow-up 15 maanden, spreiding 3-26). De mediaan van de duur van het effect in de totale groep was 4 maanden (spreiding 3-26). Dit komt overeen met onderzoeken waarin PRF wordt toegepast bij andere pijnsyndromen[11,12].

Als gevolg van deze veelbelovende resultaten is een RCT opgezet om de effectiviteit van PRF te vergelijken met een neurectomie bij ACNES patiënten die goed (maar tijdelijk) reageerden op buikwandinjecties met een lokaal anestheticum (**hoofdstuk 4**). Hierbij werden 66 patiënten gerandomiseerd voor ófwel PRF behandeling, ófwel een anterieure neurectomie, in een cross-over design. Als primaire uitkomstmaat is gekeken naar het aantal patiënten met >50% pijnreductie op basis van de NRS score na 8 weken follow-up. Secundaire uitkomstmaten waren patiënttevredenheid, kwaliteit van leven, gebruik van analgetica en optreden van bijwerkingen. Indien patiënten uit de PRF ontevreden waren met het behandelresultaat, werd er via "cross-over" alsnog een neurectomie uitgevoerd.

In **hoofdstuk 5** worden de resultaten van dit onderzoek weergegeven. In de neurectomie groep werd 61% (17/28) met succes behandeld en in de PRF groep 38% (12/32) (P>0.05). In de neurectomie groep werd echter een grotere pijnreductie dan in de PRF groep behaald (gemiddeld percentage pijnreductie -47.7 [95% betrouwbaarheidsinterval -64.8 tot -30.6] versus -24.7 [95% betrouwbaarheidsinterval -41.6 tot -7.9]; P = 0.056). Dertien patiënten uit de PRF groep konden hun geplande operatie afzeggen omdat de pijnreductie na de PRF behandeling voldoende bleek. De secundaire uitkomstmaten en bijwerkingen waren vergelijkbaar in beide groepen. Concluderend is PRF een veilige en effectieve behandeloptie bij een deel van

de ACNES patiënten bij wie conservatieve behandelingen tot dan toe ontoereikend waren. Als gevolg hiervan zou PRF als behandeloptie overwogen kunnen worden, voordat er wordt overgegaan tot chirurgische interventies.

Subtypes van ACNES

ACNES wordt waarschijnlijk veroorzaakt door beknelling van de *anterieure* huidtakken van de thoracale spinale zenuw ter hoogte van de laterale rand van de musculus rectus abdominis. Deze thoracale zenuw heeft drie verankeringspunten in het verloop van de zenuw: **(1)** aan de rugzijde waar de posterieure takken ontspringen, **(2)** in de flank waar de laterale takken ontspringen en **(3)** in de buikwand waar de anterieure takken door de rectus abdominis spier lopen[13]. Een eerder geopperde mechanische theorie suggereert dat rek op de buikwand, in combinatie met een voor zenuwen ongelukkige anatomie, leidt tot lokale ischemie van deze zenuw, met als gevolg een vicieuze cirkel van zwelling-pijn-spierspasme-ischemie-zwelling, en dientengevolge ernstige pijn op één van deze drie locaties. Hoewel het grootste deel van de patiënten dat naar SolviMáx wordt verwezen, lijdt aan ACNES dan wel liespijn, kan een kleine subpopulatie zich met net iets andere symptomen presenteren. Deze subgroepen hadden een pijnpatroon dat marginaal verschilde van ACNES. In **hoofdstuk 6** wordt een 26-jarige patiënte beschreven met chronische pijn in de *rug*, hoogstwaarschijnlijk als gevolg van beknelling van de posterieure tak van de thoracale spinale zenuw (POCNES). Een neurectomie van deze zenuw zorgde er uiteindelijk voor dat deze invaliderende pijn verdween. Na twee jaar follow-up was er nog altijd een duidelijke vermindering van de pijn. Deze klinische entiteit was tot dan toe nog niet in de literatuur beschreven. In **hoofdstuk 7** wordt een case series van 14 patiënten beschreven die gediagnosticeerd waren met POCNES. Ze werden behandeld met lokale injecties van lidocaïne en, indien de pijn toch bleef bestaan, met een neurectomie. Zeven van de elf patiënten hadden een succesvol behandelresultaat na deze operatie. Het voorgestelde behandelalgoritme leidde tot een succespercentage van 57% (mediane follow-up van 29 maanden, spreiding 5-48).

Een ander subtype van ACNES werd vastgesteld bij patiënten met chronische gelokaliseerde *flankpijn*. Er was bij deze patiënten sprake van sensibiliteitsstoornissen van de huid in de flank en een positieve Pinch test. Dit nieuwe syndroom wordt Lateral Cutaneous Nerve Entrapment Syndrome (LACNES) genoemd. In **hoofdstuk 8** worden de karakteristieken van dit pijnsyndroom beschreven en wordt een diagnostisch en behandelprotocol voorgesteld. Van de 30 patiënten die werden gediagnosticeerd met LACNES, is meer dan de helft succesvol behandeld met lokale lidocaïne injecties (mediane follow-up van 40 maanden, spreiding 2-103).

De meeste ACNES patiënten presenteren zich met éénzijdige buikwandpijn. Een opmerkelijke bevinding in de grote case series van ACNES patiënten (**hoofdstuk 1**) is dat bij één op de acht ACNES patiënten een praktisch altijd symmetrische bilaterale variant van ACNES werd aangetroffen. De hypothese is dat een complex onderliggend mechanisme van 'communicerende' zenuwbanen mogelijk ten grondslag ligt aan de bilaterale pijn. 'Mirror image sensory dysfunction' (MISD) is een fenomeen waarbij een eenzijdige perifere zenuwlaesie tot

een vergelijkbare pijnpresentatie aan de 'niet aangedane', contralaterale zijde van het lichaam leidt[14]. Contralaterale sensorische dysfunctie, gedefinieerd als neuropathische pijn zoals allodynia en hyperalgesie, kan optreden in deze geselecteerde groep patiënten[15,16]. In **hoofdstuk 9** worden de kenmerken van 146 bilaterale ACNES patiënten en hun behandelresultaten weergegeven. De patiëntkarakteristieken en bevindingen van het lichamelijk onderzoek zijn in essentie vergelijkbaar met de unilaterale variant. Het uiteindelijke succespercentage van de behandelingen is echter iets lager. Uit een literatuuronderzoek komt naar voren dat ongeveer 10% van alle ACNES patiënten een bilaterale variant heeft. Dit percentage komt grofweg overeen met het percentage (13%) dat wij hebben aangetroffen. We concludeerden dat bilaterale ACNES een complexe variant is van ACNES, waarbij het precieze onderliggend pathologisch mechanisme nog onduidelijk is.

CONCLUSIES

1. Een ACNES patiënt is meestal een vrouw van jonge of middelbare leeftijd met een gelokaliseerde abdominale pijn. De diagnose kan worden overwogen indien er sprake is van sensibiliteitsstoornissen in het gebied rondom het maximale pijnpunt, een positieve Pinch test, een positieve Carnett test en/of een positieve reactie (>50% pijnverlichting) op buikwandinfiltratie met een lokaal anestheticum.
2. Pulsed Radiofrequency (PRF) is een minimaal invasieve, veilige en haalbare behandeloptie voor ACNES patiënten.
3. PRF kan de noodzaak van een neurectomie verminderen en kan daarom worden overwogen als conservatieve behandelopties falen.
4. Bij patiënten met chronische flank- of rugpijn kunnen zorgvuldige anamnese en nauwgezet lichamelijk onderzoek via eenvoudige somatosensorische testen (huidsensibiliteit testen met een wattenstaafje, Pinch test) een neuropathisch pijnsyndroom zoals LACNES of POCNES onthullen.
5. Injectietherapie is langdurig effectief bij meer dan de helft van de LACNES patiënten.
6. Een chirurgische neurectomie voor POCNES leidt tot een succesvol behandelresultaat bij 2 van de 3 patiënten
7. Een bilateraal pijnsyndroom kan voorkomen bij 1 op de 8 patiënten met ACNES. Dit heeft vergelijkbare patiëntkenmerken en bevindingen bij lichamelijk onderzoek, maar het uiteindelijke behandelsucces is iets lager.
8. De exacte onderliggende mechanismen in de pathogenese van ‘mirror image sensory disfunction’, hetgeen leidt tot een bilaterale ACNES, moeten nog worden ontrafeld.

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Dankwoord
List of publications
Curriculum vitae auctoris

DANKWOORD

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LIST OF PUBLICATIONS

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11. **Maatman RC**, Steegers MA, Boelens OB, Lim TC, van den Berg H, van den Heuvel SA, Perquin CW, van Eerten PV, Scheltinga MR, Roumen RM**.** 'Pulsed radiofrequency (PRF) als behandeling voor anterior cutaneous nerve entrapment syndrome (ACNES)'. *Ned Tijdschr Geneeskd. 2015;159:A9682*

Oral presentations

2018	Chirurgendagen	Veldhoven
2018	NVvH / Vereniging Samenwerkende Ouder- en Patiëntenorganisaties (VSOP): Landelijk netwerk ACNES	Eindhoven
2017	International Meeting of the European Society of Surgical Research (ESSR)	Amsterdam
2017	Annual congress of the European Hernia Society (EHS)	Wenen
2017	Anesthesiologendagen	Maastricht
2017	Wetenschapsavond Máxima Medisch Centrum	Veldhoven
2016	ACNES Symposium	Veldhoven

CURRICULUM VITAE AUCTORIS

Robbert Cees Maatman was born on May, 11th 1990 in Enschede (Overijssel), the Netherlands. He soon moved to Beegden, Limburg and graduated from high school in 2008 (Gymnasium, Scholengemeenschap St. Ursula).

Shortly thereafter he started his study 'Biomedical Sciences' at the University of Hasselt, Belgium. After studying for a year on Belgian soil, he returned to Maastricht commencing his Health Sciences studies at the University of Maastricht. In the summer of 2011 his career in the medical world was launched. He completed internships in Kampala (Uganda) and London (United Kingdom) and published his first scientific article under the supervision of dr. F. Fransen, a pulmonologist at the Maastricht University Medical Center (MUMC+). He was introduced to Máxima Medical Center (MMC) in July 2014 and was inspired by the surgeons dr. R. Roumen and dr. M. Scheltinga regarding the illusive syndrome termed the Anterior Cutaneous Nerve Entrapment Syndrome (ACNES). During this internship, the cornerstone of his scientific career was laid by starting with the preparations for the present PhD thesis. In his 5th year of medical school, he completed a research protocol for the PULSE trial and successfully gained permission from The Medical Ethical Committee (METC) to start with this randomized controlled trial at the beginning of his final year of medical school. Robbert graduated in 2016 and started as a resident at the Department of General Surgery and the Emergency Department of MMC in Eindhoven/Veldhoven. Meanwhile his research on ACNES steadily continued and was combined with participating in clinical duties in the outpatient clinic of the Centre of Expertise for Abdominal Wall and Groin Pain (SolviMáx).

As of August 2018 he works as a full-time resident at the Department of General Surgery at MMC. Robbert hopes to start his surgical residency soon. He currently lives together with his girlfriend Lotte Voeten in Eindhoven.

CURRICULUM VITAE AUCTORIS

Robbert Cees Maatman werd geboren op 11 mei 1990 te Enschede (Overijssel). Al snel volgde een verhuizing naar Beegden, Limburg. Aldaar heeft hij basisschool en middelbare school doorlopen. Hij behaalde zijn Gymnasium diploma aan de Scholengemeenschap St. Ursula te Horn in 2008.

Vervolgens startte hij in 2008 met de studie 'Biomedische Wetenschappen' aan de Universiteit van Hasselt, België. Na een jaar op Belgisch grondgebied gestudeerd te hebben, keerde hij terug naar Maastricht om daar te beginnen aan de studie Gezondheidswetenschappen aan de Universiteit van Maastricht. In de zomer 2011 werd hij ingeloot voor Geneeskunde en begon zijn carrière in de medische wereld. Tijdens deze studie volgde hij coschappen in o.a. Kampala (Oeganda) en Londen (Verenigd Koninkrijk) en publiceerde hij zijn eerste wetenschappelijke artikel samen met dr. F. Fransen, longarts in het Maastricht Universitair Medisch Centrum (MUMC+). Met Máxima Medisch Centrum (MMC) maakte hij voor het eerst kennis in juli 2014. Gedurende het coschap Chirurgie werd Robbert geënthousiasmeerd voor het ACNES-syndroom door de chirurgen Rudi Roumen en Marc Scheltinga. Aansluitend aan dit coschap werd de basis voor zijn verdere wetenschappelijke carrière gelegd door te starten met de voorbereidingen voor zijn promotietraject. In jaar 5 schreef hij een METC-aanvraag voor de PULSE-trial, waarna dit onderzoeksproject kon worden gestart tijdens zijn laatste jaar van de opleiding Geneeskunde. In 2016 behaalde hij zijn artsexamen, waarna hij begon als arts-assistent op de afdeling heelkunde en de spoedeisende hulp/escalatiedienst van het MMC in Eindhoven/Veldhoven. Het onderzoek naar het ACNES-syndroom ging gestaag door en de wetenschappelijke interesse werd gecombineerd met werkzaamheden bij het Expertisecentrum voor buikwand- en liespijnsyndromen (Solvimáx).

Vanaf augustus 2018 werkt hij als fulltime ANIOS bij de heelkunde in het MMC. Robbert hoopt zijn weg binnen dit vakgebied te vervolgen en uiteindelijk opgeleid te worden tot chirurg. Hij woont momenteel samen met zijn vriendin Lotte Voeten in Eindhoven.